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Rapid generation of molecular complexity under Pd(II) and Rh(III) Catalysis

Thesis Submitted in Accordance with the Requirements of
The University of Edinburgh for the Degree of Doctor of Philosophy
By

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School of Chemistry
College of Science and Engineering
January 2015

Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the PhD degree in January 2011, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification.

Chapter 1 – Enantioselective Pd(II)-catalysed Nucleophilic Additions of 2-Alkylazaarenes contains results indicated in the following publication:

Diastereo- and Enantioselective Pd(II)-Catalyzed Additions of 2-Alkylazaarenes to *N*-Boc Imines and Nitroalkenes, Best, D.; Kujawa, S.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 18193-18196

Chapter 2 – Synthesis of Spirocyclic Enones *via* Rh(III)-catalysed C–H Functionalisations contains results indicated in the following publication:

Synthesis of Spirocyclic Enones by Rhodium-Catalyzed Dearomatizing Oxidative Annulation of 2-Alkenylphenols with Alkynes and Enynes, Kujawa, S.; Best, D.; Burns, D. J.; Lam, H. W. *Chem. Eur. J.* **2014**, *20*, 8599-8602

Signed

Szymon Kujawa

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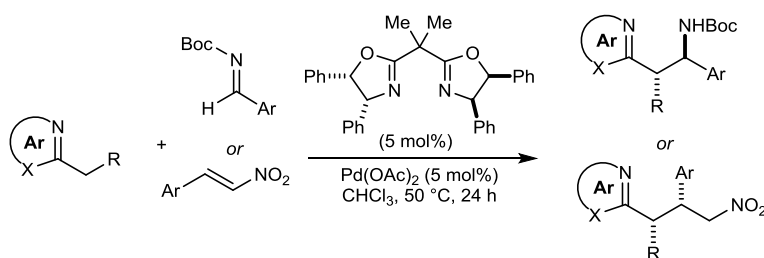
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Kochana Mamo i Tato! Tę pracę dedykuję Wam! Dziękuję, za wszystko!!!

ABSTRACT

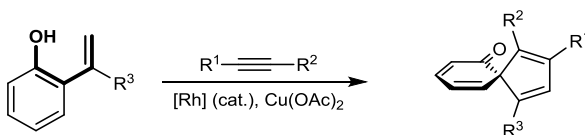
1. Enantioselective Pd(II)-Catalysed Nucleophilic Additions of 2-Alkylazaarenes

The first project deals with enantio- and diastereoselective palladium(II)-catalysed nucleophilic additions of 2-alkylazaarenes to *N*-Boc imines and nitroalkenes. Under the optimised reaction conditions high levels of diastereo- and enantioselection of the addition products were achieved. Introduction of the electron-withdrawing group at the aryl ring of the substrate allows running the reaction under mild, experimentally convenient reaction conditions. The new described method allows the enantioselective synthesis of 2-(β -aminoalkyl)azaarenes, which are substructures found in drug candidates molecules for the treatment of type 2 diabetes and schizophrenia.



2. Synthesis of Spirocyclic Enones via Rh(III)-Catalysed C-H Functionalisation

The second project describes the synthesis of spirocyclic enones by rhodium(III)-catalysed dearomatising oxidative annulation of 2-alkenylphenols with alkynes and 1,3-enynes. A good to high yield with great regioselectivity was obtained. The further synthetic utility of the product was also investigated and led to the formation of highly functionalised tetracycles *via* 1,6 conjugation addition reaction.



List of abbreviations

μ w	microwave
AAA	asymmetric allylic alkylation
acac	acetylacetonate
Ar	aryl
BARF	Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BBN	9-Borabicyclo[3.3.1]nonyl
BiPy	bipyridine
Boc	<i>tert</i> -butoxycarbonyl
Box	bisoxazoline
Bz	benzoyl
C	Celsius
calcd	calculated
cat.	catalyst
cod	1,5-cyclooctadiene
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
d	doublet
DCE	1,2-dichloroethane
DG	directing group
DMF	N,N-dimethylformamid
DME	1,2-dimethoxyethane

DMSO	dimethyl sulfoxide
DPP	diphenylphosphoroso
dppp	1,3-Bis(diphenylphosphino)propane
dr	diastereomeric ratio
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
E	electrophile
ee	enantiomeric excess
ESI	electrons spray ionisation
equiv.	equivalent
EWG	electron-withdrawing group
fur	furyl
Het	heterocycle
Hex	hexyl
HMDS	hexamethyldisilazide
HRMS	high resolution mass spectrometry
IR	infrared spectroscopy
L _n	ligand
m	multiplet
<i>m</i>	<i>meta</i>
M	metal
Mes	mesityl
Mg	milligram

MHz	megahertz
MIDA	<i>N</i> -methylinodiacetyl
Min	minute(s)
mL	millilitre
m.p.	melting point
MS	molecular sieves
NMR	nuclear magnetic resonance spectroscopy
Ns	<i>para</i> -nitrobenzenesulfonyl
Nu	nucleophile
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
PEPPSI-IPr	[1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
PMB	<i>para</i> -methoxybenzyl
Pin	pinacol
Piv	pivaloyl
PMB	<i>para</i> -methoxy benzyl
PMHS	polymethylhydrosiloxane
ppm	parts per million
Pr	propyl
q	quartet
<i>rac</i>	racemic

<i>rr</i>	regioisomeric ratio
RT	room temperature
s	singlet
SDS	sodium dodecyl sulfate
t	triplet
<i>t</i> -AmOH	<i>tert</i> -amyl alcohol
TBS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilyl
THF	tetrahydrofuran
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetate
TLC	thin layer chromatography
TMDS	tetramethyldisiloxane
TMS	trimethylsilyl
TPPDS	triphenylphosphine-3, 3', 3''-diphenylsulfonic acid dipotassium salt
Ts	tosyl
<i>t</i>	<i>tert</i> (iary)
UV	ultraviolet spectroscopy

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1. ENANTIOSELECTIVE PD-CATALYSED NUCLEOPHILIC ADDITIONS OF 2-ALKYLAZAARENES TO *N*-BOC IMINES AND NITROALKENES

1.1 INTRODUCTION

Heteroarenes are important chemical motifs which are present in many natural products, agrochemicals or industry due to their physical, chemical and biological properties.^{[1],[2]} They are often used as building blocks for the development of new medicines and drugs (Figure 1.1).^{[3],[4],[5]}

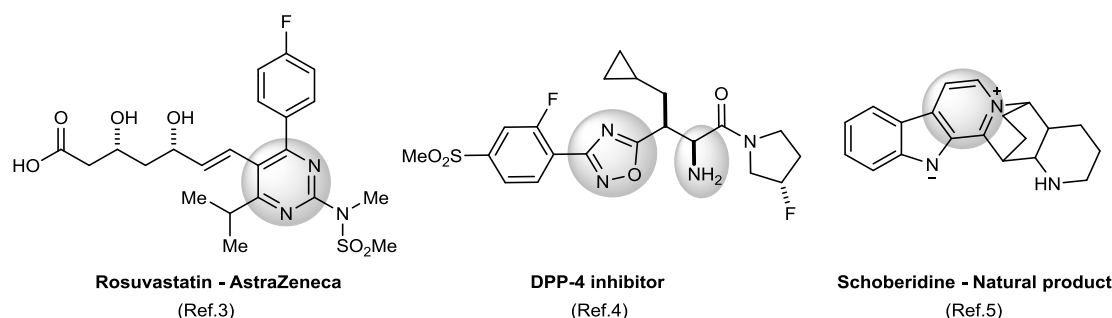
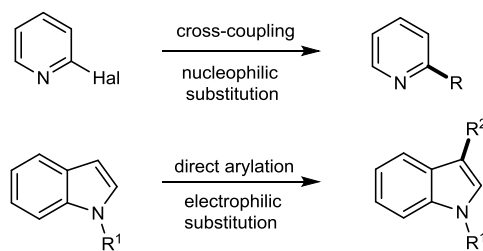


Figure 1.1: Natural products and drugs containing heterocycles.

Synthetic methods that enable functionalisation of azaarenes and their derivatives such as cross-coupling reactions, direct arylation, electrophilic and nucleophilic substitution (Scheme 1.1),^{[6],[7]} are very useful for generating new C–C bonds. Addition reactions of electron-rich azaarenes containing an embedded enamine moiety, such as indoles and pyrroles, to π -electrophiles have been extensively studied and can provide the addition product in an enantioselective fashion (e.g. Friedel-Crafts alkylation).^[8] However, with regards to asymmetric functionalisation of electron- poor azaarenes with an imine-embedded motif, the existing methodologies provide the product in good yield but chirality is often not generated. Therefore, the development of new and effective enantioselective methodologies is highly desirable.





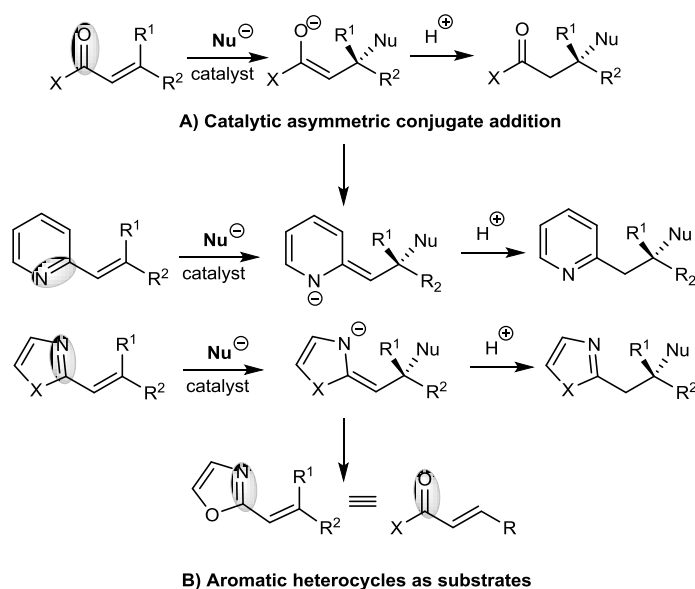
Scheme 1.1: Existing synthetic methodologies.

This part of the thesis will be focused on asymmetric addition reactions of various nucleophiles to alkenylazaarenes. Recent studies towards activation of alkylazaarenes in nucleophilic additions reactions to π -deficient electrophiles which delivered enantio- and diastereoselective products will be described. Presented examples describing the mode of activation by azaaarenes in asymmetric catalysis are based on the work done within our group,^[9] supported with a brief overview of existing literature.

1.1.1 CATALYTIC ENANTIOSELECTIVE NUCLEOPHILIC ADDITIONS TO 2-ALKENYLAZAARENES

One of the fundamental C–H/C–C bond forming reactions is the transition-metal catalysed 1,4-addition of a nucleophile to an alkene activated by an adjacent electron-withdrawing group (Scheme 1.2A). As this type of reaction has been widely studied racemically and enantioselectively to synthesise molecules of interest,^[10] our group questioned whether having a C=N moiety of a heteroarene adjacent to an alkene could provide similar effective activation towards nucleophilic attack for asymmetric conjugate addition reactions (Scheme 1.2B). In other words, can the C=N moiety act as a carbonyl equivalent? If the answer to this question is yes, then, the addition of the nucleophile could proceed *via* temporary loss of aromaticity. Finding the catalytic system which could provide this challenging mode of activity was at that time of high interest within our group.

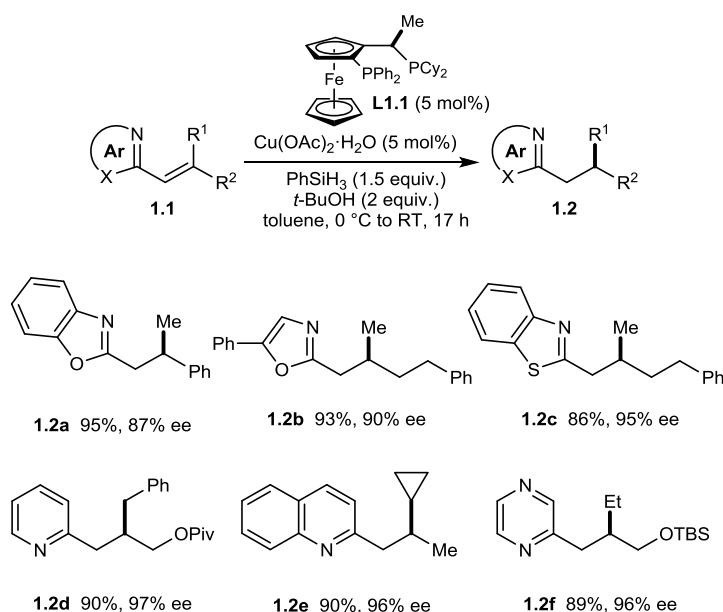




Scheme 1.2: Conjugate addition reactions.

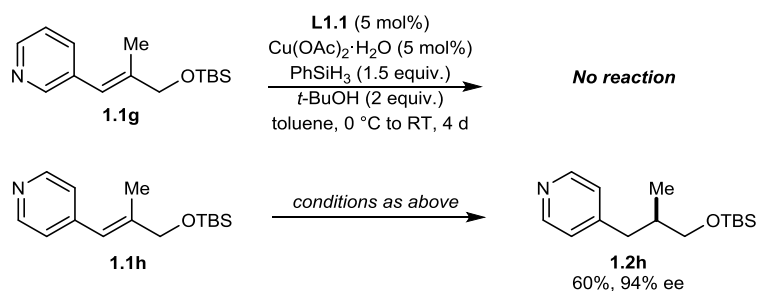
Based on well-established copper hydride reductions^{[11],[12]} of various activated alkenes, α,β -unsaturated carbonyl compounds, nitriles, sulfones, phosphonates and nitro compounds, interest in β,β -disubstituted alkenylazaarenes as conjugate reductive substrates arose in the Lam group. It was hoped that the embedded C=N moiety of an azaarene adjacent to an alkene would be sufficiently activating for this sterically hindered starting material to form a new C–H bond in an enantioselective fashion. By treating 2-alkenylazaarenes **1.1** with a chiral copper-hydride catalyst, the group demonstrated an effective method for highly enantioselective catalytic 1,4-reduction of these compounds (Scheme 1.3).^[13] The reaction is generally applicable for azaarenes such as (benz)oxazoles (**1.2a** and **1.2b**), benzothiazole (**1.2c**), pyridine (**1.2d**), quinoline (**1.2e**), and pyrazine **1.2f**). Moreover, the incorporation of various functional groups, such as esters (**1.2d**), cyclopropanes (**1.2e**), and silyl ethers (**1.2f**) at the β -positions of the alkene was well tolerated.





Scheme 1.3: Enantioselective Cu–H conjugate reduction of various β,β -disubstituted 2-alkenylazaarenes.^[13]

In order to explain and understand the success of this reaction, some control experiments were conducted with regards to 3-alkenyl- **1.1g** and 4-alkenylpyridine **1.1h**. Conjugation of the alkene with the C=N moiety is necessary for the reaction to occur, however the nitrogen does not have to be directly adjacent to the alkene moiety (Scheme 1.4). The reduction of 3-alkenylpyridine **1.1g** failed under the optimised conditions, whereas 4-alkenylpyridine **1.1h** gave the desired product in good yield and high enantioselectivity (Scheme 1.4).

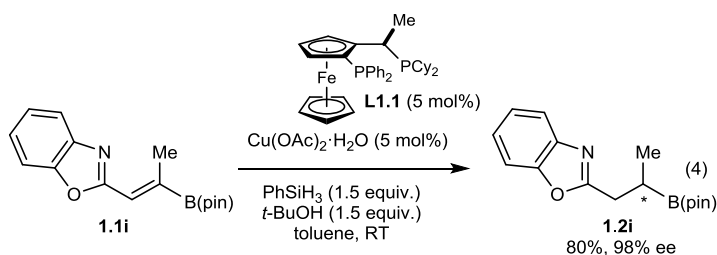


Scheme 1.4: Control experiment showing the necessity of conjugation of the alkene to a C=N moiety.^[13]

Following this work on copper-catalysed 1,4-reduction, the group of Yun and co-workers investigated the reaction of 2-vinylboronate benzoxazole **1.1i** (Scheme 1.5).^[14] Under Lam's reported conditions^[13] they showed the formation of a chiral



boronic ester **1.2i** in 98% ee. Changing the reaction conditions from PhSiH₃ in toluene to polymethylhydrosiloxane (PMHS) in THF resulted in slightly higher yield 88% but the enantioselectivity dropped to 96%.



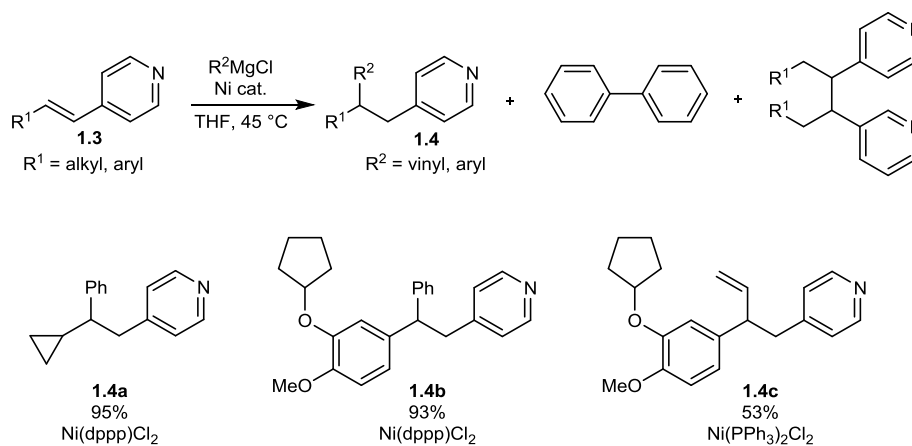
Scheme 1.5: Enantioselective Cu–H reduction of 2-vinylboronate benzoxazole **1.1i**.^[14]

To conclude, the copper-catalysed 1,4-reduction of β,β -disubstituted alkenylazarenes is an excellent way of delivering chiral alkylazaarenes enantioselectively. However, the possibility to form a new C–C bond *via* nucleophilic addition of a carbon nucleophile to β -monosubstituted alkenylazarenes would be more suited for the convergent synthesis of compound libraries.

In 1933, the group of Hoffman, Farlow and Fuson showed that stoichiometric amounts of Grignard reagents can be successfully added to 2-[(*E*)-2-phenylethenyl]quinoline proving that the embedded C=N moiety can facilitate nucleophilic addition.^[15]

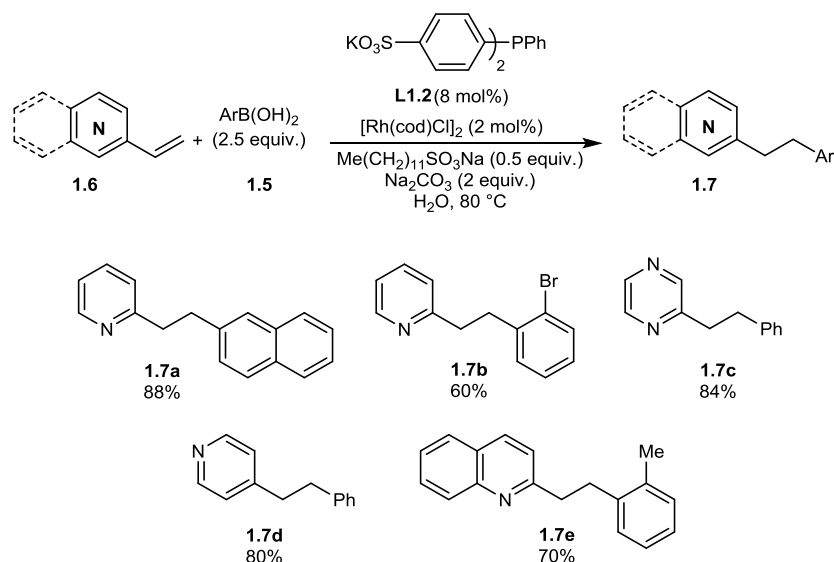
In 1998, Houpis and co-workers presented the first catalytic addition of aryl and vinyl Grignard reagents and zincates to β -substituted 4-vinylpyridines **1.3**. The racemic addition products **1.4** were obtained in good to high yields (Scheme 1.6).^[16] Studies involving the effect of temperature on the process showed that it was necessary to heat the reaction to 45 °C directly after the Grignard addition to reduce formation of a biphenyl by-product and symmetrical dimers. Similar yields were obtained with phenyl zincate reagent ($\text{PhZnMe}_2\text{MgCl}$) with even less formation of biphenyl by-product. Unfortunately, efforts towards developing an enantioselective variant of this reaction did not succeed. After intensive screening of various classes of chiral ligands such as diamines, bisphosphines, bis-sulfonamides, aminoalcohols and diols the ee's ranged from 0–15%.





Scheme 1.6: Additions of organometallic reagents to 4-vinylpyridines **1.3** catalysed by Ni-complexes.^[16]

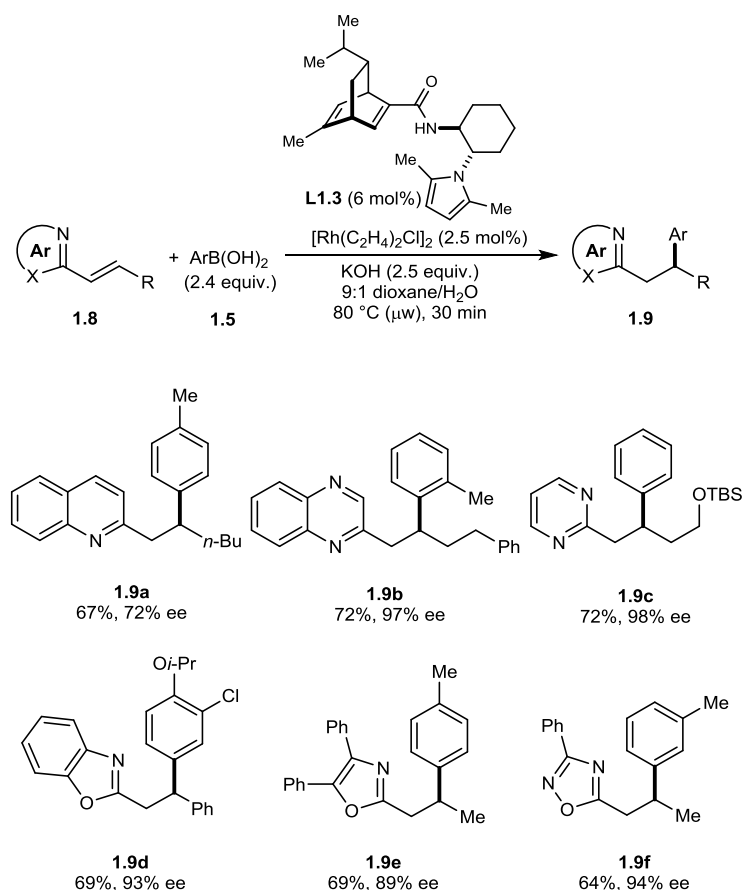
The Rh-catalysed 1,4-nucleophilic addition to activated alkenes is well developed and commonly used in organic synthesis. In 2001 Lautens and co-workers described the first rhodium-catalysed addition of boronic acids **1.5** to vinylazaarenes **1.6** under aqueous conditions (Scheme 1.7).^[17] The combination of a water-soluble phosphine ligand TPPDS **L1.2** and $[\text{Rh}(\text{cod})\text{Cl}]_2$ was crucial for the reaction to succeed. In organic solvents the conversion was less than 10%. The addition of sodium dodecyl sulfate (SDS) was required to suppress protodeboronation of the aryl boronic acid and also accelerated the reaction rate.



Scheme 1.7: Addition of aryl boronic acids **1.5** to vinylazines **1.6** under rhodium catalysis.^[17]

Compared to vinylazaarenes, this process is more challenging for β -substituted alkenylazaarenes. Introduction of an additional substituent decreases the reactivity of an alkene due to steric hindrance but if the reaction works, formation of a chiral product may be achieved. This approach was described by the Lam group and co-workers in 2010. They found that by employing chiral diene **L1.3** (6 mol%) and $[\text{Rh}(\text{C}_2\text{H}_4)\text{Cl}_2]_2$ (2 mol%), highly enantioselective additions of arylboronic acids **1.5** to β -monosubstituted alkenylazaarene **1.8** were possible (Scheme 1.8).^[18] The reaction was promoted by microwave irradiation in 9:1 dioxane/ H_2O in the presence of KOH, which was crucial for improving the conversion. In terms of substrate scope, various arylboronic acids were tolerated (including methyl, chloro, isopropyl substituents at the phenyl ring). Various activating groups were also effective such as quinoline (**1.9a**), quinoxaline (**1.9b**), pyrimidine (**1.9c**), benzoxazole (**1.9d**), diphenyloxazole (**1.9e**), and oxadiazole (**1.9f**) in delivering the product in good to high yields and enantioselectivity.

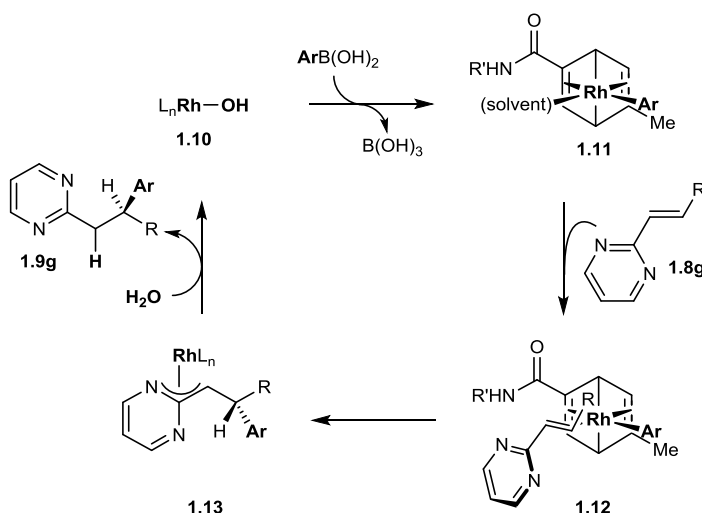




Scheme 1.8: Enantioselective Rh-catalysed arylation of β -monosubstituted alkenylazaarenes.^[18]

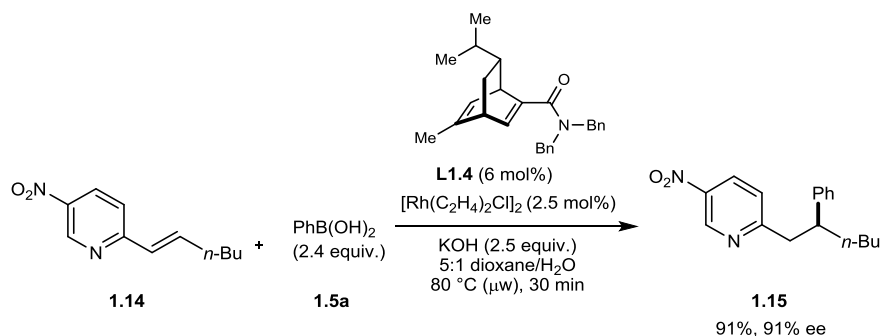
The proposed catalytic cycle for this process is based on Hayashi's studies on the conjugate addition of arylboronic acids to enones.^[19] For the mechanistic explanation, an illustrative example of 2-alkenylpyrimidine **1.8g** is presented in Scheme 1.9. The chiral diene-ligated rhodium hydroxide **1.10** is formed in the first step, which then undergoes transmetalation with arylboronic acid to generate rhodium aryl species **1.11**. The rhodium-aryl linkage is positioned *trans* to the more electron-deficient alkene. Coordination of the alkenylazaarene **1.8g** to the binding site of the rhodium-aryl species **1.11** occurs as depicted in **1.12** to minimise unfavourable non-bonding interactions between the heteroarene and the amide substituent of the ligand. Arylrhodation of the bound substrate results in the formation of aza- π -allylrhodium intermediate **1.13**, which then undergoes hydrolysis to regenerate the rhodium hydroxide **1.10** and liberate the product **1.9g**.





Scheme 1.9: Proposed mechanism of rhodium-catalysed conjugate addition of arylboronic acids to β -monosubstituted alkenylazaarenes^[18]

When the reaction of 2-vinylpyridine was performed, a complex mixture of by-products was obtained. However, further studies within our group showed that the introduction of a strongly electron-withdrawing nitro group at the 5 position of the 2-alkenylpyridine **1.14** increases the reactivity dramatically, allowing 1,4-arylation of these type of compounds.^[20] Good yield and enantioselectivity was obtained when the combination of $[(\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}_2)]_2$ (2.5 mol%) and chiral ligand **L1.4** (6 mol%) was used (Scheme 1.10).

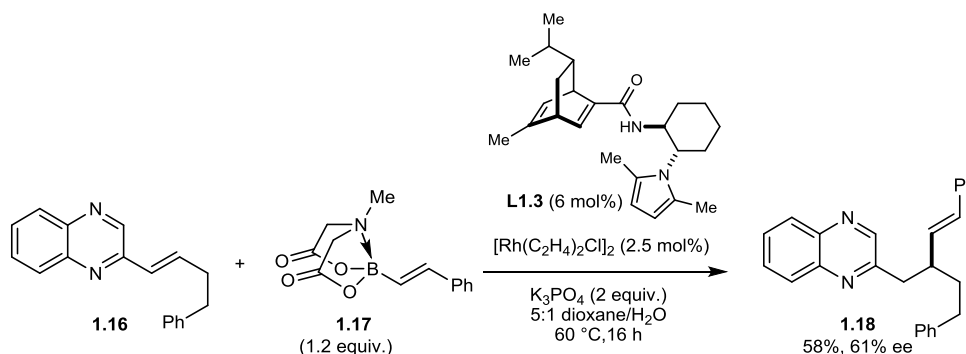


Scheme 1.10: Arylation of 5-nitro-2-alkenylazaarene **1.14** under rhodium catalysis.^[20]

Attempts to broaden the reaction scope and alkenylate β -monosubstituted azaarenes using boronic acids failed due to their instability and formation of protodeboronated by-products. One way to overcome this problem is to use alkenyl MIDA boronates which are benchtop-stable compounds. Furthermore, they are able to gradually

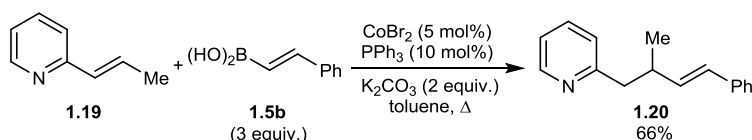


release the boronic acid *in situ* under controlled aqueous basic conditions to prevent decomposition pathways. Rhodium-catalysed reaction of alkenylquinoxaline **1.16** and (*E*)-2-phenylvinyl MIDA boronate **1.17** in 5:1 dioxane/H₂O in the presence of K₂CO₃ (2.0 equiv.) at 60 °C for 16 h gave the alkenylated product **1.18** in 58% yield and 61% ee (Scheme 1.11).



Scheme 1.11: Alkenylation of alkenylquinoxaline **1.16** with MIDA boronate **1.17**.^[20]

Simultaneously, the group of Yorimitsu and Oshima published their work on cobalt-catalysed addition of styrylorganoboron reagents to vinylpyridines.^[21] One of the racemic examples presented in their studies is the reaction of 2-[(1*E*)-1-propenyl]pyridine **1.19** with (*E*)-2-phenylethenylboronic acid **1.5b** to give the addition product **1.20** in 66% yield (Scheme 1.12).

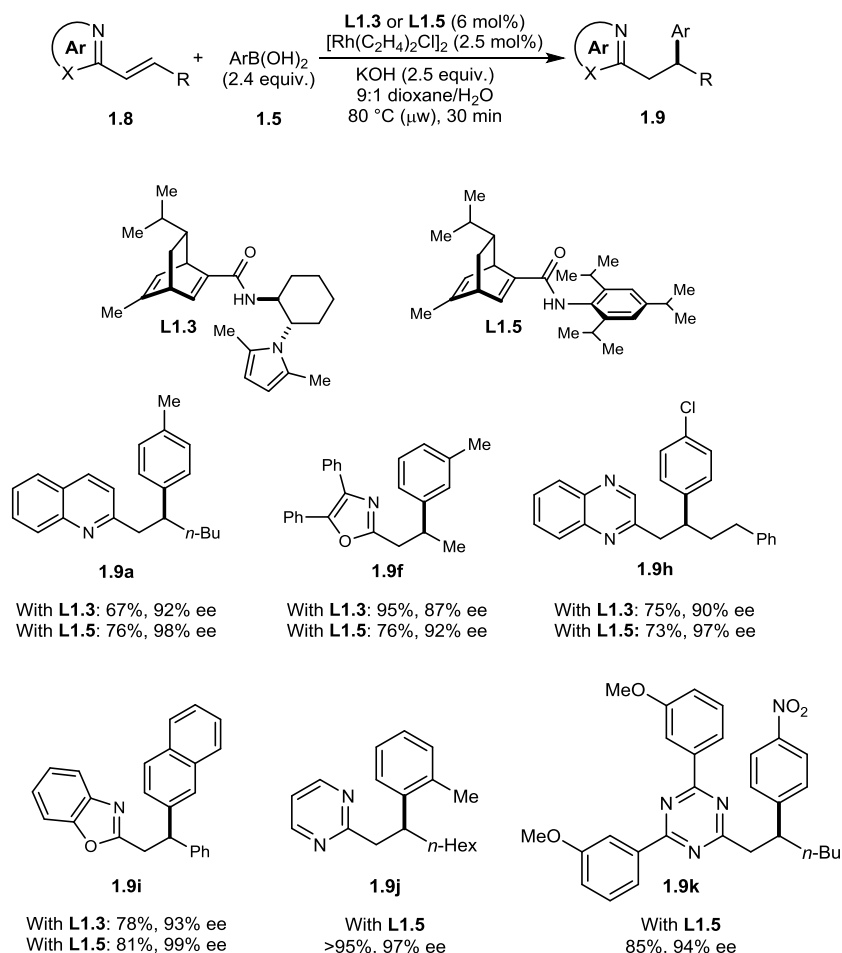


Scheme 1.12: Alkenylation of propenylpyridine **1.19** under cobalt catalysis.^[21]

The Lam group has recently shown that a second-generation chiral diene ligand **L1.5**,^[22] containing a 2,4,6-triisopropylanilide moiety, gives superior results compared with previously described ligand **L1.3** in arylation processes with 2-alkenylazaarenes **1.8**.^[18] Furthermore, the synthesis of the ligand **L1.5** is simpler than of ligand **L1.3** as its structure is less complex. The results of addition products with the two different ligands are summarised in Scheme 1.13. In general, higher enantioselectivities were obtained with ligand **L1.5**. Under optimised conditions,



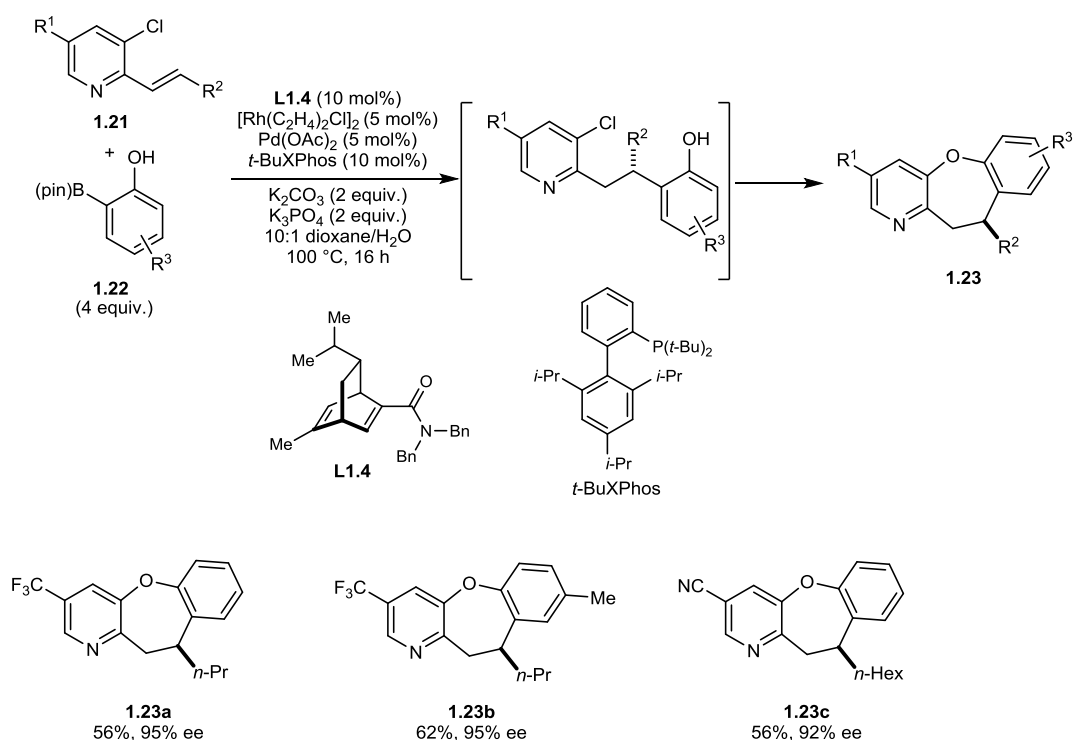
arylation of 2-alkenylazaarenes proceeded smoothly with a range of arylboronic acids **1.5**. The reaction was also efficient for various activating groups such as quinolines (**1.9a**), (benz)oxazoles (**1.9f** and **1.9i**), pyrimidines (**1.9h** and **1.9j**), or triazoles (**1.9k**).



Scheme 1.13: Comparison of ligand **L1.5** with **L1.3** in enantioselective arylation reactions of β -monosubstituted alkenylazaarenes **1.8** and boronic acids **1.5**.^[22]

In 2013, Lautens and co-workers published the synthesis of azadihydrodibenzoxepine **1.23** via a two-step domino reaction strategy, involving a Rh-catalysed arylation of β -monosubstituted vinylpyridines **1.21**, followed by a Pd-catalysed C–O bond formation (Scheme 1.14).^[23]

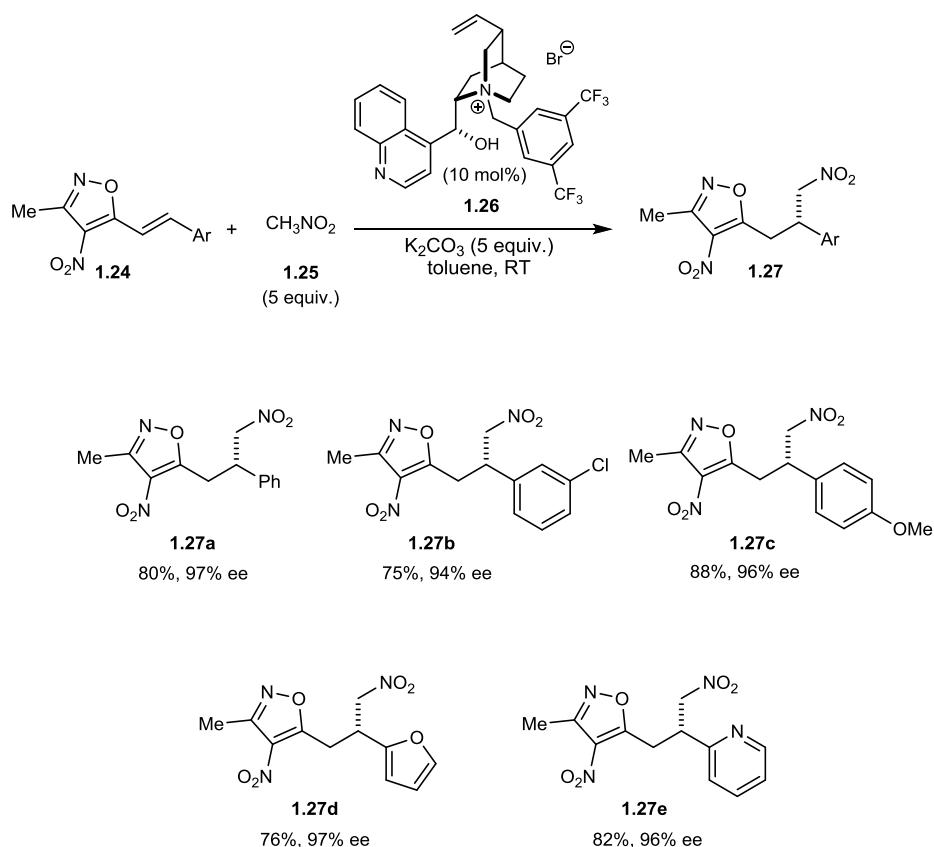




Scheme 1.14: Synthesis of aza-dihydrodibenzoxepines **1.23** using an enantioselective domino process.^[23]

Organocatalytic reactions have also been explored for asymmetric nucleophilic additions to 2-alkenylazaarenes. This type of conjugate addition reaction was published by the groups of Bernardi and Adamo in 2009. They showed that nitromethane **1.25** can be successfully added to 5-styrylisoxazoles **1.24** under chiral phase-transfer catalysis **1.26** (Scheme 1.15).^[24] Substituents containing various functional groups such as chloro or methoxy at the aromatic ring were tolerated and gave compounds **1.27b** and **1.27c** with 94% ee and 96% ee, respectively. Further investigation revealed that this process was also efficient with heteroaryl substituents at the β -position of the 5-styrylisoxazole compounds **1.27d** and **1.27e**.

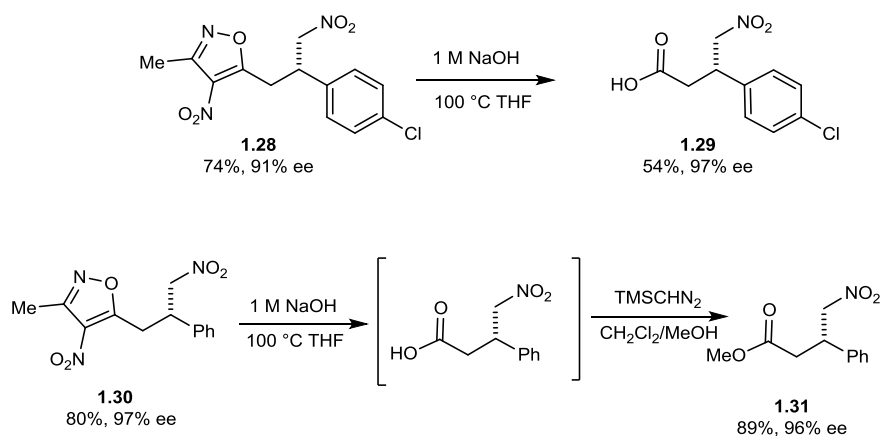




Scheme 1.15: Enantioselective conjugate additions of nitromethane **1.25** to 5-styrylisoxazole **1.24**.^[24]

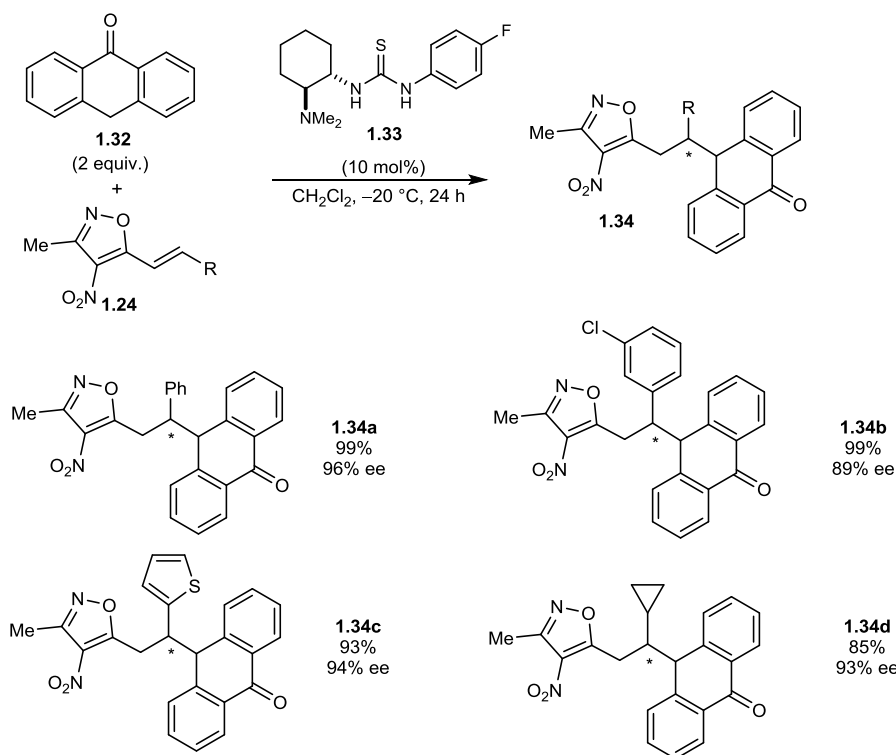
This methodology provided a range of very interesting Michael addition products which could be functionalised further to give γ -nitrocarboxylic acid **1.28** or ester **1.31** (Scheme 1.16). The isoxazole ring opening of product **1.28** was achieved under basic conditions (1 M NaOH) to provide the carboxylic acid **1.29**. Similarly, the addition product **1.30** was functionalised to give the acid derivative which was subsequently treated with $TMSCHN_2$ in MeOH to provide the ester **1.31**.





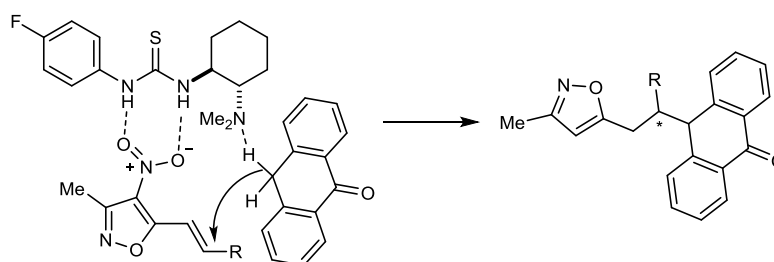
Scheme 1.16: Further product manipulation by isoxazole ring opening under basic conditions.^[24]

Further studies by the group of Sun and co-workers, regarding 3-methyl-4-nitro-5-alkenylisoxazoles **1.24** as cinnamate equivalents, revealed that in the presence of chiral thiourea catalyst **1.33**, anthrone **1.32** can be enantioselectively added to **1.24** to give complex products **1.34** (Scheme 1.17).^[25] Various substituents were tolerated at the alkenyl position of the isoxazole such as phenyl **1.34a**, *meta*-chloro **1.34b**, heteroaryl **1.34c** and cyclopropanyl **1.34d** giving the Michael product with good to high yield and stereoselectivity.



Scheme 1.17: Enantioselective addition of 3-methyl-4-nitro-5-alkenylisoxazoles **1.24** to anthrone **1.32** using thiourea catalyst **1.33**.^[25]

Dual reactivity of the thiourea-tertiary amine catalyst is believed to be responsible for the success of this reaction. The activation of a nucleophile (anthrone **1.32**) happens through the deprotonation by the basic residue of the catalyst. Simultaneously, the thiourea moiety is responsible for the activation of the electrophile (5-styrylisoxazole **1.24**) *via* double-hydrogen bonding with the nitro group (Scheme 1.18).

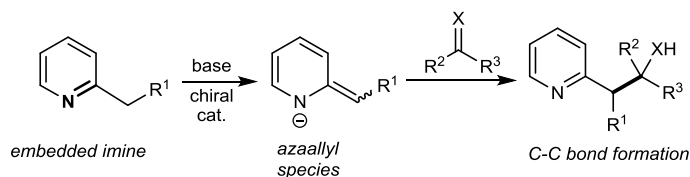


Scheme 1.18: Proposed transition state for the enantioselective 1,6-Michael addition of 5-styrylisoxazole **1.24** to anthrone **1.32** catalysed by **1.33**.^[25]

In summary, a number of transition-metal catalysed and organocatalytic reactions in which 2-alkenylazaarenes act as electrophiles have been developed in recent years. As described in this section the embedded C=N moiety may act in a similar way to a carbonyl group in facilitating 1,4-addition reactions. The substrate scope is quite broad as includes vinyl, β -mono- and β,β -disubstituted alkenyazaarenes.

1.1.2 2-ALKYLAZAARENES AS PRONUCLEOPHILES IN C-C BOND FORMING REACTIONS

As demonstrated in the first part of the introduction, azaarenes play an important role as activating groups for alkenes towards nucleophilic addition. In 2011, we became interested in 2-alkylazaarenes as potential pronucleophiles in C–C bond forming reactions. We wondered if the embedded C=N moiety could act similarly to a carbonyl group and acidify the α -proton to form an azaallyl anion. Introduction of an electrophile would provide an addition product *via* C–C bond formation (Scheme 1.19). In other words, can an azaenolate anion act as an enolate equivalent in nucleophilic addition reactions?

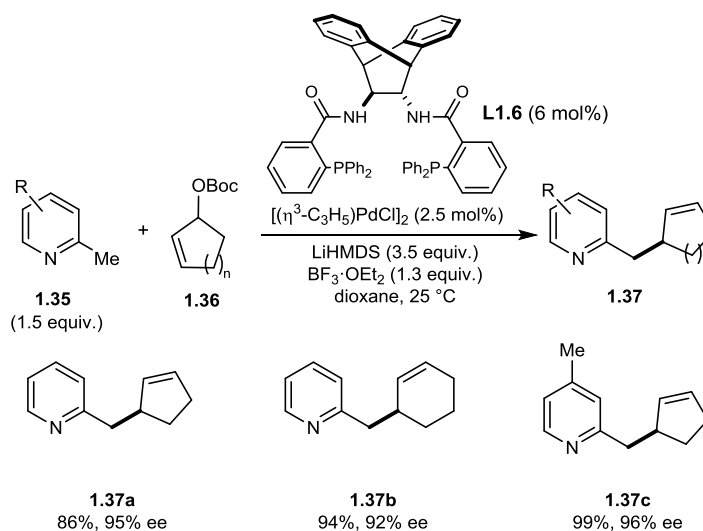


Scheme 1.19: 2-Alkenylazaarenes as pronucleophiles.

1.1.2.1 Asymmetric allylic alkylation of 2-alkylazaarenes

The group of Trost and co-workers had investigated a Pd-catalysed asymmetric allylic alkylation (AAA) reaction of 2-alkylazaarenes with π -electrophiles.^{[26],[27],[28]} In 2008, they published their work regarding a Pd-catalysed process of 2-methylpyridines **1.35** with cyclic *tert*-butyl carbonates **1.36** resulting in the synthesis of a range of molecules **1.37** containing an alkene functionality in the final structures (Scheme 1.20).^[26]

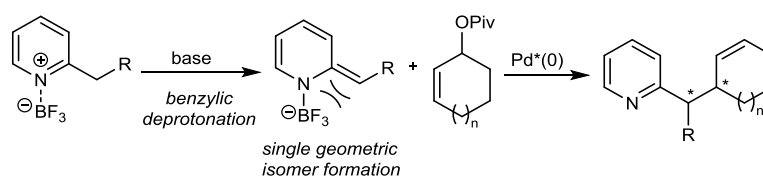




Scheme 1.20: Pd-catalysed asymmetric allylic alkylation of 2-methyl pyridyl nucleophiles **1.35** with Boc-protected cyclic alcohols **1.36**.^[26]

The studies revealed that the employment of the Lewis acid $\text{BF}_3 \cdot \text{OEt}_2$ was necessary to “soften” 2-methylpyridine **1.35** and make it more prone for the deprotonation using non-nucleophilic base, LiHMDS.

A year later, Trost and co-workers published an extension of their work regarding more substituted 2-alkylpyridines.^[27] They envisioned that due to coordination of $\text{BF}_3 \cdot \text{OEt}_2$ to the nitrogen of the pyridine, the deprotonation of the starting material would only form a single geometric isomer due to the steric hindrance. If that would be the case, the final product should be obtained with high diastereo- and enantiocontrol (Scheme 1.21).

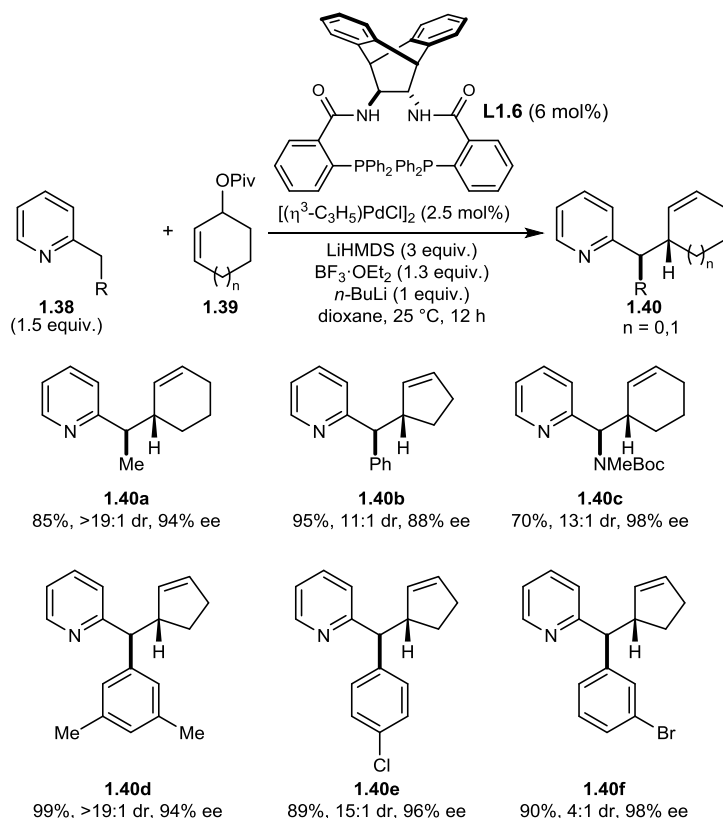


Scheme 1.21: Plausible mechanism for AAA of 2-alkenylpyridines with pivalate carbonates under Pd-catalysis.

Previously described reaction conditions that were used in AAA of 2-methyl pyridyl nucleophiles **1.35** (Scheme 1.20) were applied for more substituted alkylazaarenes **1.38**, with the addition of 1 equivalent of *n*-BuLi, which was necessary for reaching



full conversion. The authors suggest that *n*-BuLi deprotonates HMDS, which is formed due to deprotonation of the α -proton of the starting material (Scheme 1.22). In general, substrates containing 2-alkyl and 2-aryl substituents at the pyridine ring were very well tolerated (compounds **1.40a**, **1.40b**, **1.40d–f**) as well as heteroatom-containing compound **1.40c**, forming a new C–N stereocentre. Furthermore, compound **1.40f** containing an aryl bromide moiety did not undergo oxidative addition with Pd(0) or lithium-halogen exchange with *n*-BuLi.

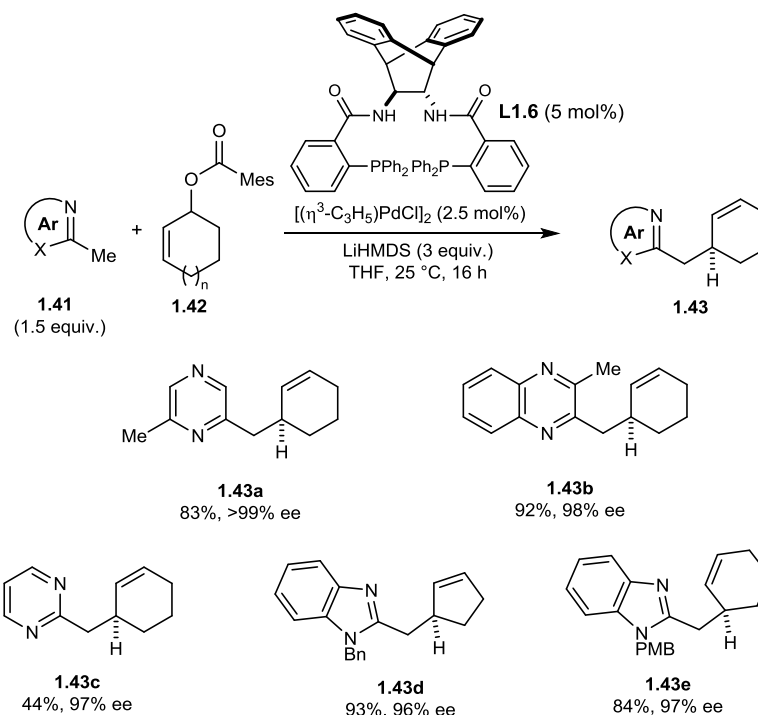


Scheme 1.22: AAA of 2-substituted alkyl pyridines **1.38** with cyclic pivalate esters **1.39**.^[27]

Further investigation by Trost and co-workers led to the development of a general method which can be used not only for 2-alkyl pyridines but a wide range of polyheteroaromatics **1.41** (Scheme 1.23).^[28] Their observations proved that substrate preactivation using $\text{BF}_3 \cdot \text{OEt}_2$ is not necessary for compounds containing more than one C=N moiety. Moreover, the reaction does not require *n*-BuLi as an additional external base, for complete conversion. Changing the leaving group for a more bulky mesityl ester was crucial to prevent deacylation of the electrophile. Under these



strongly basic conditions, neither the formation of cyclohexadiene nor doubly alkylated product was observed.

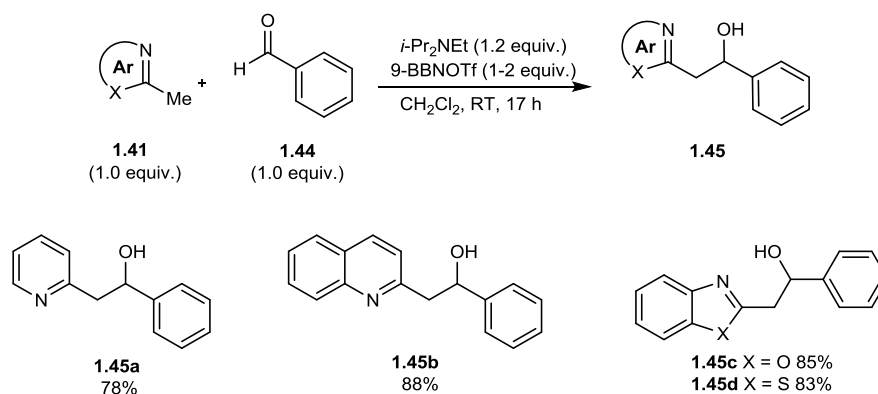


Scheme 1.23: AAA of polyheteroaromatics **1.41** with cyclic mesylate esters **45** under Pd catalysis.^[28]

Although, the described methodologies provided a wide range of interesting azaaromatics in good to high yields and enantio- and diastereoselectivities, formation of a nucleophile required the introduction of a strong base and an activating reagent in some cases. The possibility of using milder reaction conditions, from a synthetic point of view, would be of high interest.

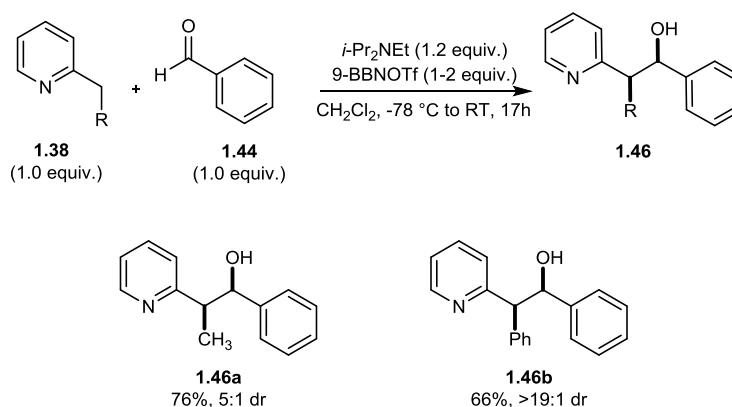
The first attempts to run this type of reaction under milder reaction conditions were reported in 1983 by the group of Hamana.^[29] They reported an aldol-type reaction of 2-methyl azaarenes **1.41** with benzaldehyde **1.44** using 9-BBN triflate as an activating reagent and diisopropylethylamine as an external base (Scheme 1.24).





Scheme 1.24: Aldol-type reaction of 2-methyl azaarenes **1.41** with benzaldehyde **1.44**.^[29]

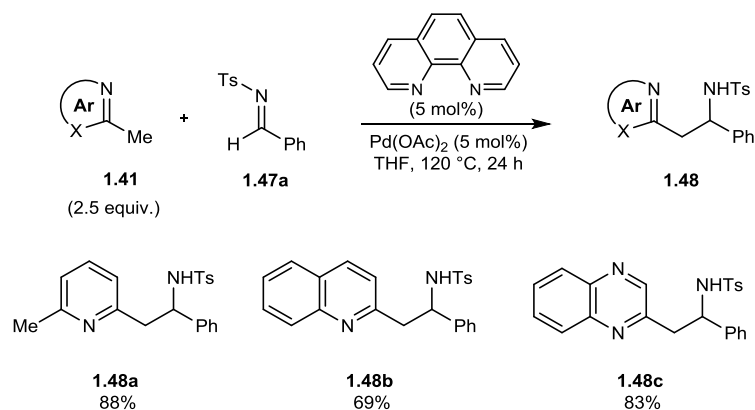
Further investigation towards stereoselective variants of this reaction revealed the aldol-type products could be obtained in good to high yield and high *syn* diastereoselectivity under the same conditions (Scheme 1.25).^[30] Enantioselective variants of this reaction had not been described.



Scheme 1.25: Stereoselective synthesis of **1.46** in the reaction of 2-substituted pyridines **1.38** with benzaldehyde **1.44**.^[30]

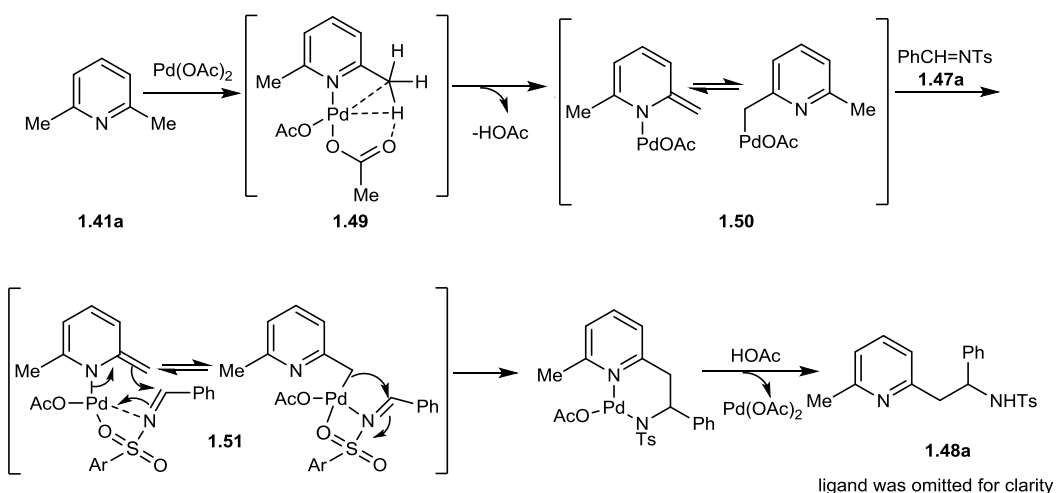
Until 2010 not much progress had been made in activation of 2-alkylazaarenes pronucleophiles under mild conditions. In 2010, the group of Huang and co-workers reported the Pd-catalysed nucleophilic addition of 2-methylazaarenes **1.41** to *N*-tosyl imines **1.47a** (Scheme 1.26).^[31] In the presence of the Lewis acid Pd(OAc)₂, 1,10-phenanthroline and polar solvent THF, the reaction proceeded smoothly giving high yields of the addition products **1.48**.





Scheme 1.26: Nucleophilic addition of 2-methylazaarenes **1.41** to *N*-tosyl imine **1.47a** under Pd-catalysis.^[31]

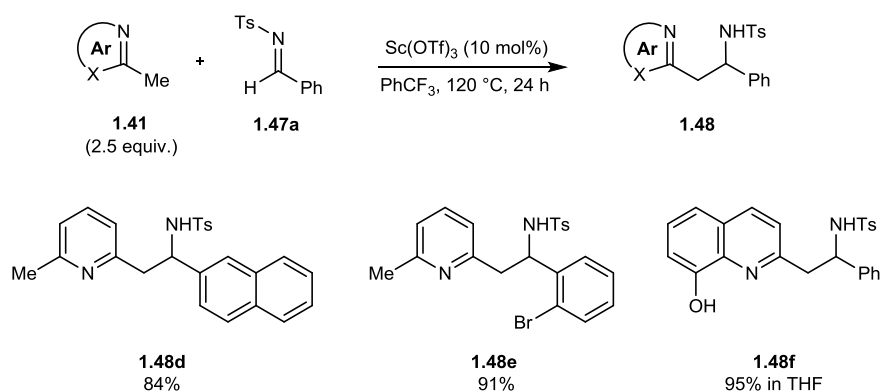
The role of Pd(OAc)₂ is shown in Scheme 1.27. It is believed that Pd(OAc)₂ coordinates to 2,6-lutidine **1.41a** to generate complex **1.49**. Then, deprotonation of the methyl group occurs by one of the acetates, forming species **1.50** and acetic acid. Coordination of the imine **1.47a** gives intermediate **1.51** which then undergoes nucleophilic addition to furnish the final product **1.48a**.



Scheme 1.27: Plausible mechanism for Pd-catalysed nucleophilic additions of 2-methylazaarene **1.41a** to *N*-tosyl imine **1.47a**.^[31]

Further investigation of this methodology was described by the same group in 2010.^[32] They showed that replacing the Lewis acid Pd(OAc)₂ with Sc(OTf)₃ and using trifluorotoluene instead of THF at 120 °C provided an easy access to a series of heterocycle-containing amines **1.48** (Scheme 1.28).

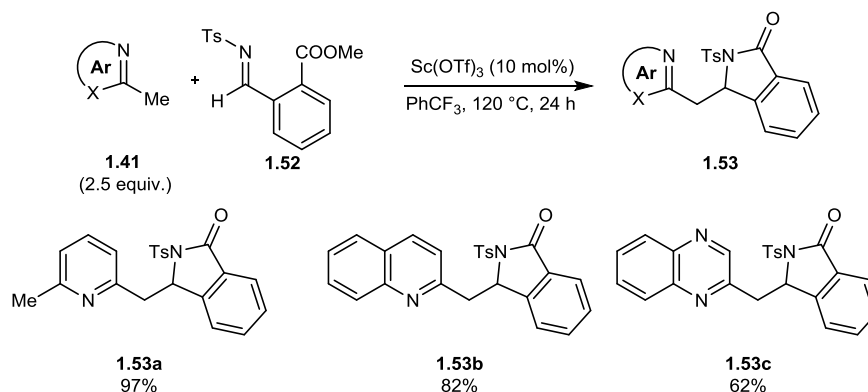




Scheme 1.28: Sc-catalysed nucleophilic additions of 2-substituted azaarenes **1.41** to *N*-sulfonyl aldimines **1.47a**.^[32]

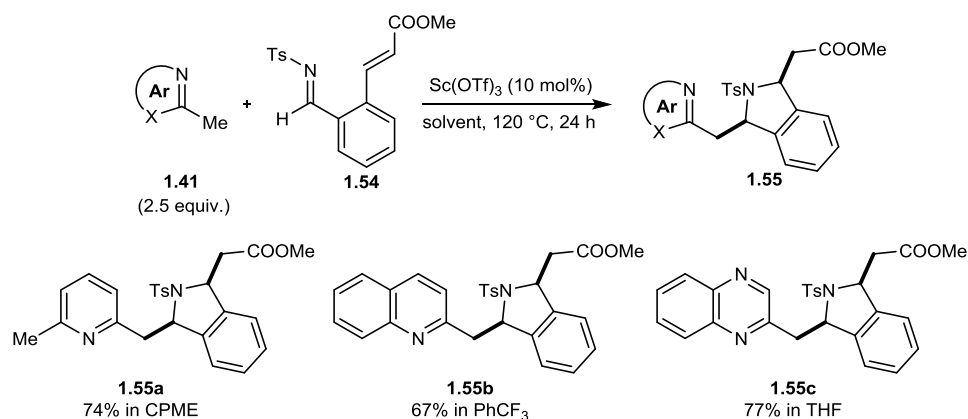
The proposed mechanism is analogous to the previously postulated Pd(II)-catalysed process (Scheme 1.27).

These reaction conditions were also used to provide a broad range of 3-substituted isoindolinones **1.53** in a one-pot fashion (Scheme 1.29). Formation of the desired product consists of a two-step process, intermolecular nucleophilic addition of 2-substituted azaarene **1.41** to *N*-tosyl imine **1.52** followed by an intramolecular amidation reaction.



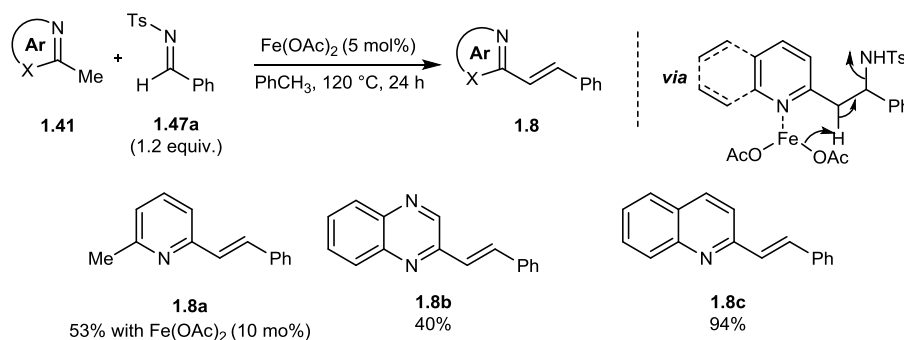
Scheme 1.29: Synthesis of 3-substituted isoindolinones **1.53** under Sc-catalysis.^[32]

A further example of this tandem process allowed the synthesis of various isoindolines **1.55** as single diastereoisomers, by applying bifunctional electrophile **1.54** (Scheme 1.30). Formation of the addition product is followed by an intramolecular aza-Michael reaction.



Scheme 1.30: Diastereoselective synthesis of isoindolines **1.55** from 2-methyl azaarenes **1.41** with *N*-tosyl imine **1.54** under Sc-catalysis.^[32]

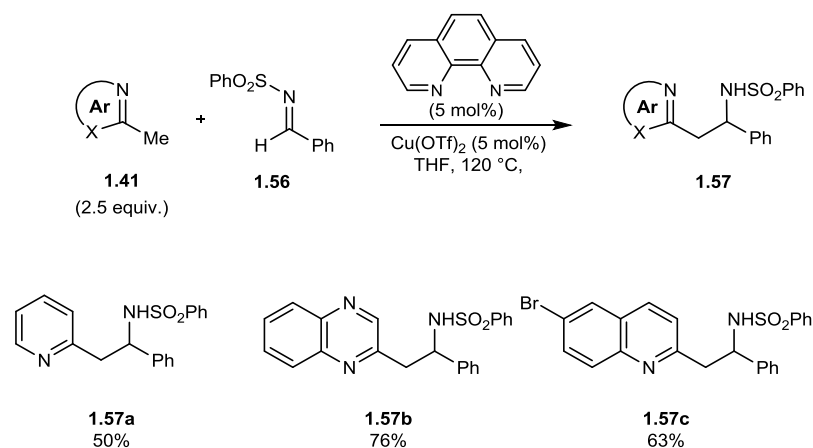
A year later, the same group discovered a new way of delivering 2-alkenylazaarenes **1.8** via alkenylation of 2-alkylazaarenes **1.41**.^[33] This process involves Fe-catalysed nucleophilic addition of 2-methyl azaarenes **1.41** to *N*-tosyl imines **1.47a** followed by elimination of the *N*-tosyl group to furnish the final product **1.8** (Scheme 1.31). Moreover, the group of Wang showed that the formation of the 2-alkenylazaarenes **1.8** is also possible when the reaction is run at reflux in toluene in the absence of Lewis acid.^[34] Recently, Xiao and co-workers also reported a catalyst-free synthesis of 2-alkenylazaarenes **1.8** but in the reaction of 2-methylquinoline with aromatic aldehydes in 1,4-dioxane.^[35]



Scheme 1.31: Synthesis of 2-alkenylazaarenes **1.8** under Fe-catalysis.^[33]

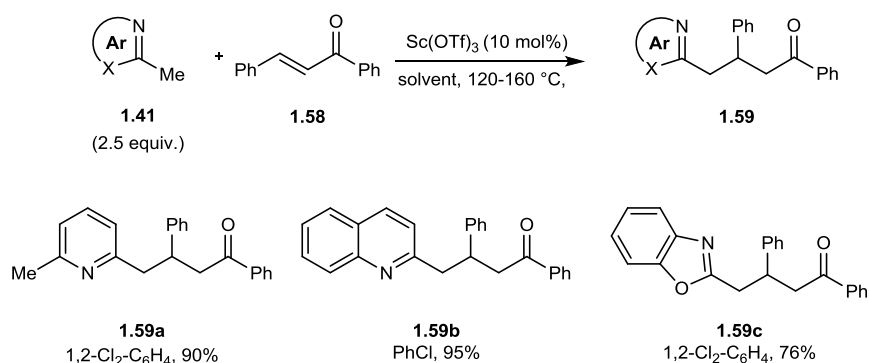
Similar results to those presented by Huang and co-workers were published by Rueping and Tolstoluzhsky.^[36] They showed that reaction of 2-methylalkylazaarenes **1.41** with *N*-sulfonyl protected aldimines **1.56** catalysed by $\text{Cu}(\text{OTf})_2$ can provide the addition product **1.57** with good to high yields (Scheme 1.32).





Scheme 1.32: Cu-catalysed addition of 2-methylazaarenes **1.41** to *N*-sulfonyl imines **1.56**.^[36]

An extension of this methodology was presented in work of Matsunaga and Kanai where 2-methyl-substituted azaarenes **1.41** were coupled with enones **1.58** under Sc(OTf)_3 catalysis (Scheme 1.33).^[37]



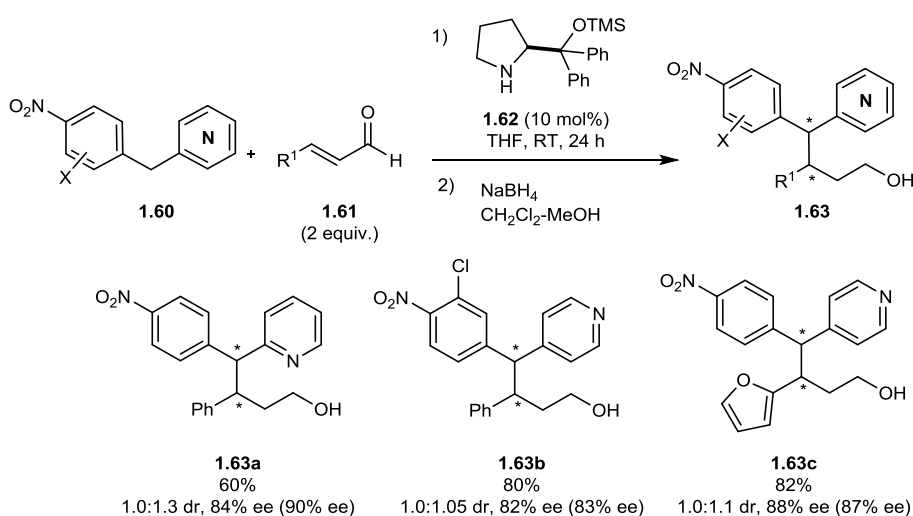
Scheme 1.33: Sc-catalysed addition of 2-methyl azaarenes **1.41** to enone **1.58**.^[37]

In summary, it has been shown that 2-alkyl-substituted azaarenes can be used as nucleophiles under acid-catalysed conditions and can be successfully added to various electrophiles such as *N*-sulfonyl imines and enones. However, all of the presented examples highlighted problems regarding the development of an enantioselective variant. First the reversibility of this process,^[34] second, the harsh reaction conditions (high temperature and long reaction times necessary to obtain high yields) and finally, the background reaction.



1.1.3 INTRODUCTION OF A SECONDARY ACTIVATING GROUP AT THE REACTING CENTRE

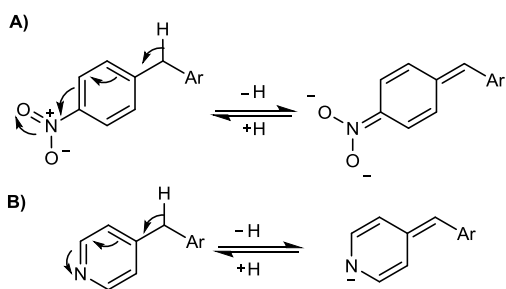
Introduction of a secondary activating group at the reacting centre of 2-alkyl azaarenes allows the reaction to proceed under milder conditions and led to the development of an enantioselective variant of the Michael process. Melchiorre and co-workers showed that the reaction of nitrobenzyl pyridines **1.60** with enals **1.61** catalysed by chiral secondary amine **1.62** can provide a range of Michael addition products **1.63** in good to high yield and enantioselectivity (Scheme 1.34).^[38] Poor diastereoselectivity was reported 1.2-1.4:1, however an easy isolation of both diastereoisomers by flash chromatography was possible.



Scheme 1.34: Asymmetric nucleophilic addition of nitrobenzyl pyridines **1.60** to enals **1.61** with chiral organocatalyst **1.62**.^[38]

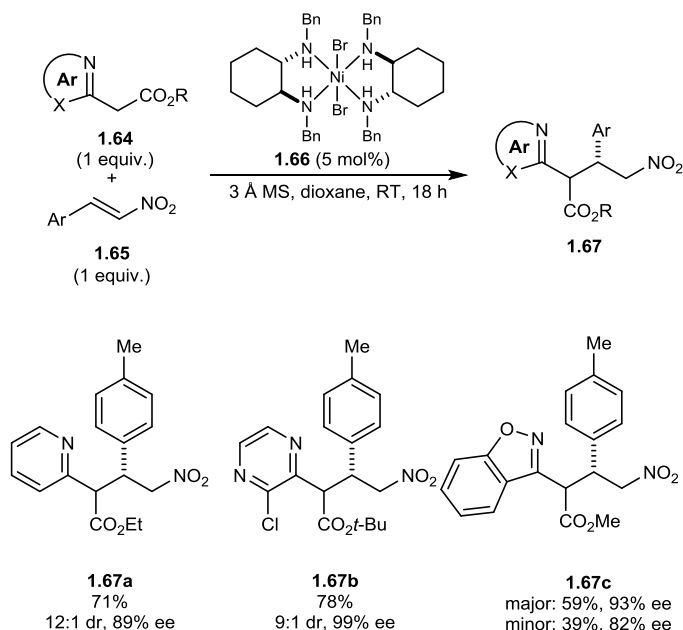
This reaction progresses smoothly when pyridine and nitrobenzyl are attached to a methylene centre. As shown below, two effects are taking place in order to activate the nucleophile: stabilisation of the anion through conjugation to the nitro group (Scheme 1.35A) and with the heteroaryl substituent (Scheme 1.35B).





Scheme 1.35: Pro-nucleophilic activation *via* delocalisation with NO₂ (A) and heteroaryl (B).

A similar approach was considered at that time by the Lam group. They wondered if the employment of an ester as the acidifying group would increase the reactivity of alkylazaarenes. They found that azaarylacetates **1.64** underwent enantioselective nucleophilic addition to nitroalkenes **1.65** in the presence of a chiral nickel(II)-bis(diamine) complex **1.66** to give the Michael products **1.67** in good to high yields, dr's and ee's. Unfortunately, some of the products tend to epimerise *via* enolisation under the optimised conditions due to the high acidity of the proton at the α-position to the ester group (Scheme 1.36).^[39]

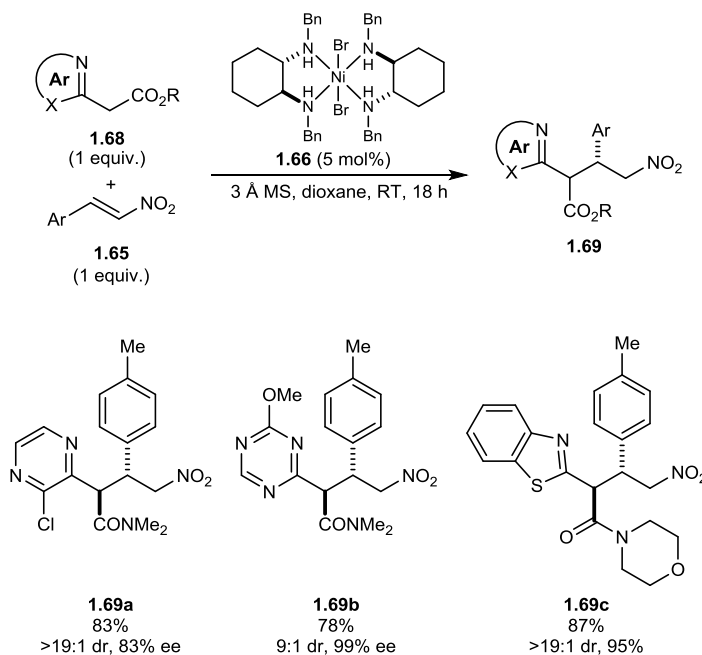


Scheme 1.36: Asymmetric nucleophilic Michael additions of azaarylacetates **1.64** to nitroalkenes **1.65** under Evans nickel complex **1.66**.^[39]

Next, azaarylamides **1.68** were examined in order to broaden the reaction scope (Scheme 1.37). In comparison to the azaarylacetate products **1.67**, those derived from



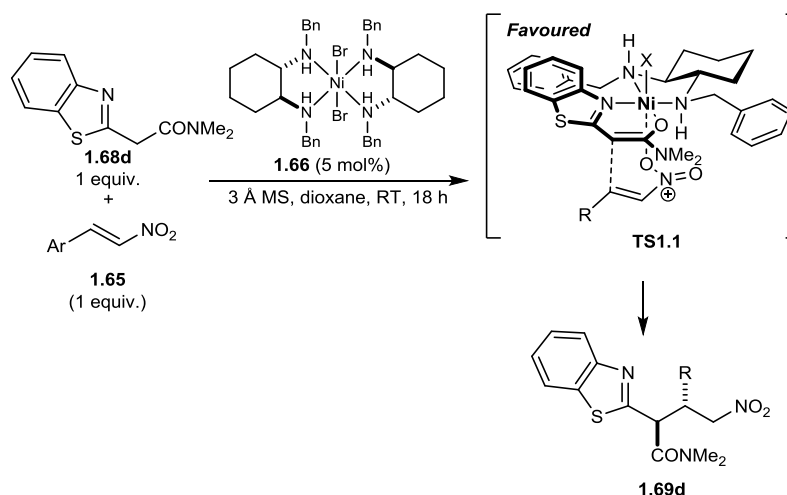
azaarylamides **1.69** did not undergo enolisation at the α -position to the stereogenic tertiary amides, due to A_{1,3} strain.^[40]



Scheme 1.37: Ni-catalysed azaarylamides **1.68** nucleophilic addition to nitroalkenes **1.65**.^[39]

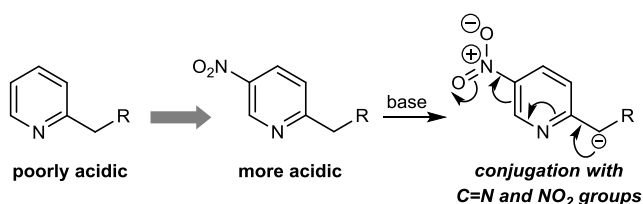
Based on previously reported mechanistic studies of the diamine ligand by the Evans group,^[41] Lam *et al.* proposed a stereochemical model to explain the diastereo- and enantioselectivity of these reactions. For illustrative purposes benzothiazole amide **1.68d** is chosen. The proposed model is based upon the following assumptions: 1) one of the diamine ligands is fully displaced from the catalyst **1.66** by the starting material. The free ligand then deprotonates the metal-bound azaarylamide. 2) The oxygen of the formed enolate and the azaarene nitrogen coordinate to the nickel centre. 3) The nitroalkene **1.65** is bound to nickel to stabilise the developing negative charge of the nitronate anion. Thus, the described reactions by Lam and co-workers go through **TS1.1** which is free of unfavourable interactions and it is consistent with the experimentally observed outcome of this process (Scheme 1.38).





Scheme 1.38: Stereochemical model for the reaction outcome.^[39]

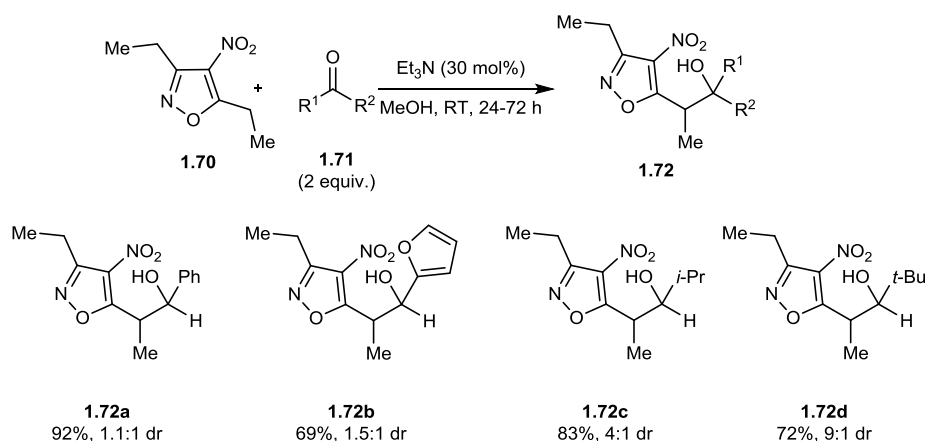
Activation of alkylazaarenes can be also achieved when an electron-withdrawing group is installed on the azaarene such that conjugation with the C=N moiety is still possible. This allows resonance stabilisation of the anion which is formed by α -deprotonation of the azaarene (Scheme 1.39).



Scheme 1.39: Pro-nucleophile activation *via* introduction of an electron-withdrawing group.

Based on this hypothesis the group of Adamo and co-workers described a new variant of the Henry reaction between 3,5-diethyl-4-nitroisoxazoles **1.70** and carbonyl compounds **1.71**. The reaction proceeded in the presence of 30 mol% of triethylamine in methanol giving the addition product **1.72** in high yield and low to moderate diastereoselectivities (Scheme 1.40).^[42] The products delivered from (hetero)aryl aldehydes tended to epimerise more readily in comparison with alkyl-derived products due to the higher acidity of the methylene group. Compounds **1.72a** and **1.72b** were then obtained in a low diastereomeric ratio.



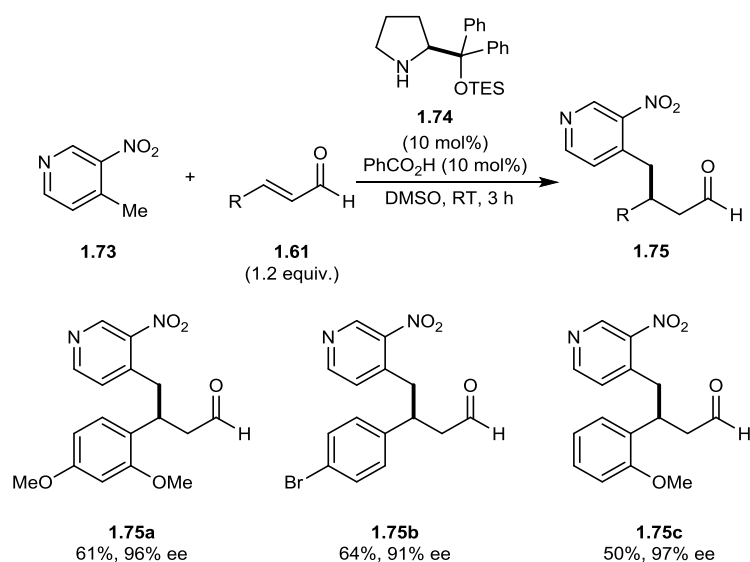


Scheme 1.40: Henry reaction of 3,5-diethyl-4-nitroisoxazoles **1.70** and aldehydes **1.71** under mild basic conditions.^[42]

Our group had also applied this strategy in the process of enantio- and diastereoselective nucleophilic addition of 2-alkylazaarenes with *N*-Boc imines and nitroalkenes.^[43] The detailed studies regarding this process can be found in the Results and Discussion Part of this thesis (See Section 1.3).

The group of Li and Wang^[44] also later showed that the employment of the strongly electron-withdrawing nitro group can alter the electronic properties of the alkylazaarenes in order to activate the benzylic position towards the nucleophilic attack. The reaction of 4-methyl-3-nitropyridines **1.73** with α,β -unsaturated aldehydes **1.61** catalysed by the diphenylprolinol diethyl silyl ether **1.74** *via* iminium catalysis led to the enantioselective formation of a new C–C bond generating compounds **1.75** (Scheme 1.41).

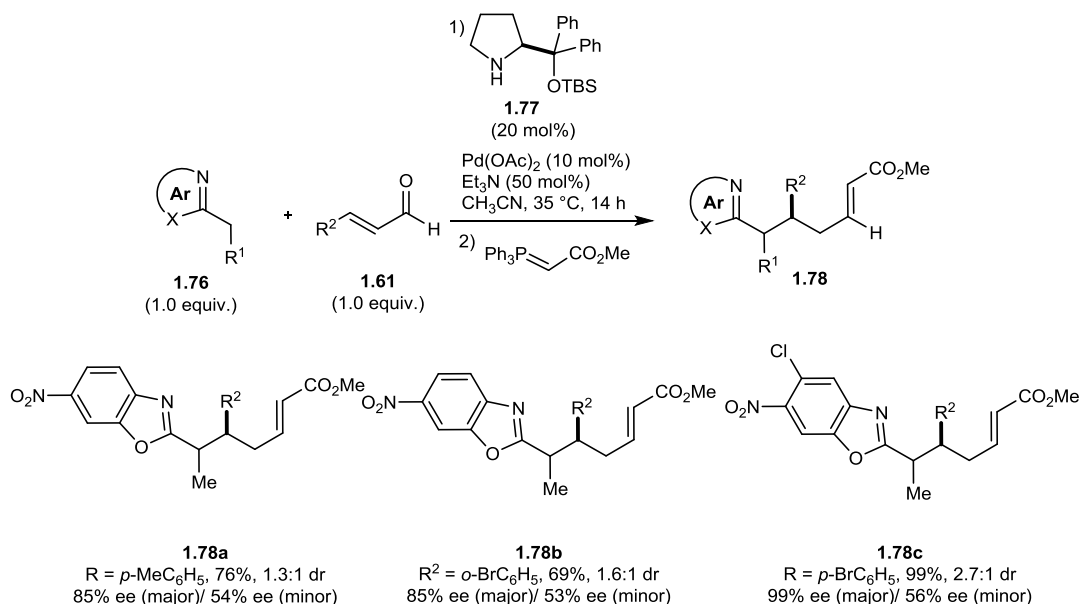




Scheme 1.41: Enantioselective Michael additions of 4-methylazaarenes **1.73** to enals **1.61** with proline-derived organocatalyst **1.74**.^[44]

The group of Rios and co-workers investigated this area further and showed that nitro-substituted alkylazaarenes **1.76** can be added to enals **1.61** in the presence of proline-derived chiral catalyst **1.77**. However, as the formed product was found to be unstable, subsequent manipulation was required that led to formation of the Wittig product **1.78** (Scheme 1.42).^[45]





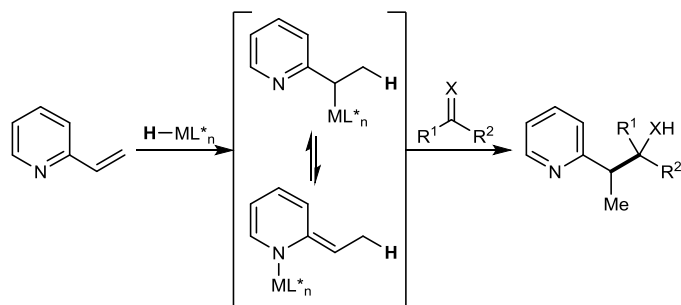
Scheme 1.42: Synthesis of **1.78** after Michael addition and Wittig reaction.^[45]

In summary, a few examples were presented where activated alkylazaarenes undergo nucleophilic additions to various electrophiles such as α,β -unsaturated carbonyl compounds, imines and nitroalkenes. The reactions work under relatively mild conditions only if the second activating group is either attached to the reacting centre or to the azaarene itself.

1.1.4 2-ALKENYLАЗAARENES AS LATENT NUCLEOPHILES IN ADDITION REACTIONS

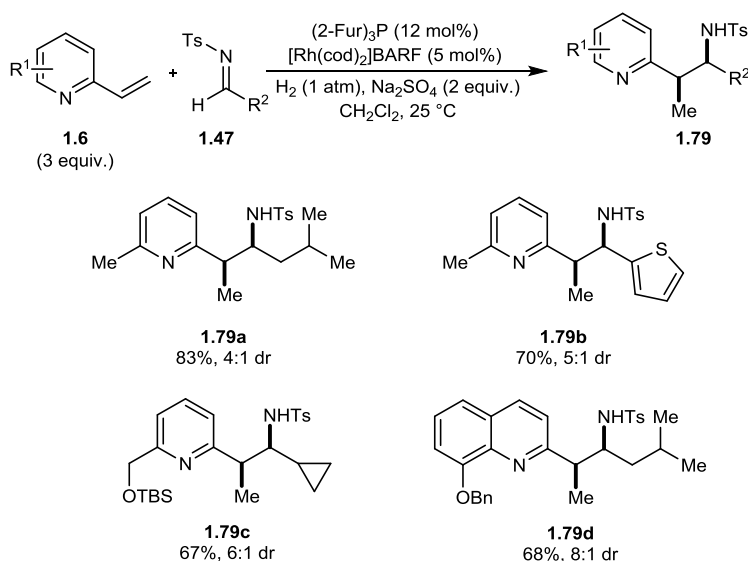
As discussed in the previous section, formation of a nucleophile from 2-alkylazaarenes *via* α -deprotonation provides the formation of an azaallylmetal intermediate which reacts with an electrophile to form a new C–C bond. Another approach which provides these types of species is the hydrometallation of 2-alkenylazaarenes under mild reaction conditions (Scheme 1.43).





Scheme 1.43: Formation of an azaallyl metal intermediate from 2-alkenylazaarenes.

The group of Krische described the first metal-catalysed reductive coupling of vinyl azines **1.6** with *N*-sulfonyl imines **1.47** to give the final pyridinylsulfone amide product **1.79** as a single regio- and diastereoisomer (Scheme 1.44).^[46] The catalytic system of 5 mol% [Rh(cod)₂]BARF catalyst, 12 mol% phosphine ligand, and 2 equivalents of Na₂SO₄ as an imine hydrolysis suppressor was efficient in the reaction of 6-substituted vinylazines with *N*-sulfonyl imines. However, under the optimised reaction conditions, 2-vinylpyridine which lacks a substituent at the 6-position, failed in generating the final product due to strong coordination at nitrogen.



Scheme 1.44: Rh-catalysed reductive coupling of vinyl azaarenes **1.6**.^[46]

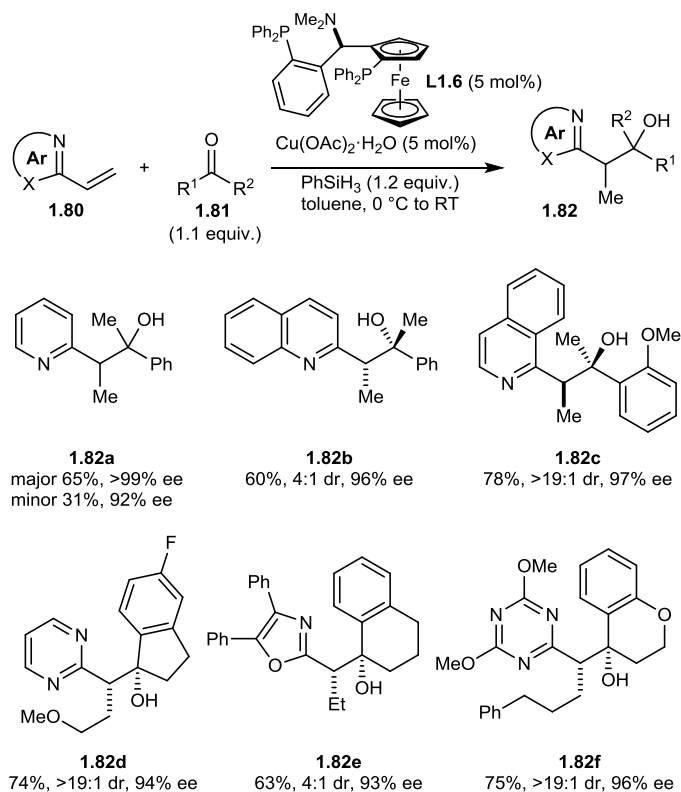
The Lam group previously described enantioselective copper-catalysed reductions of β,β -disubstituted alkenylazaarenes that led to the formation of chiral alkylazaarenes (Section 1.1.1, Scheme 1.3),^[13] This reaction proceeds *via* organocopper species



which are then quenched with *t*-BuOH to furnish the final product. Based on the proposed mechanistic explanation, they wondered if the organocopper species could be trapped with a π -electrophile instead of a proton. The investigation revealed that various vinyl azaarenes **1.80** underwent enantioselective copper-catalysed reductive coupling with ketones **1.81**, using PhSiH₃ as the stoichiometric hydride source. The Taniaphos ligand **L1.6** was found to be the most effective chiral bisphosphine ligand among those screened in delivering the products in high enantio- and diastereoselectivities (Scheme 1.45).^[47] Various heterocycles were tolerated such as pyridines (**1.82a**), (iso)quinolines (**1.82b–c**), pyrimidines (**1.82d**), diphenyloxazoles (**1.82e**) and triazines (**1.82f**). Furthermore, β -substituted azaarenes were also effective in this process (**1.82e–f**). With respect to ketones both acyclic and cyclic were successful coupling partners.

The stereochemistry of the final products is dependent on the structure of the starting materials. Different stereochemistry was generated even though the same enantiomer of the ligand **L1.6** was used in this reaction (see (iso)quinoline-derived products **1.82b** and **1.82c** to compare). Similarly, the stereochemical outcome is different for acyclic and cyclic ketones (see examples **1.82b–c** and **1.82e–f**). The reasoning is not fully understood at the present time.

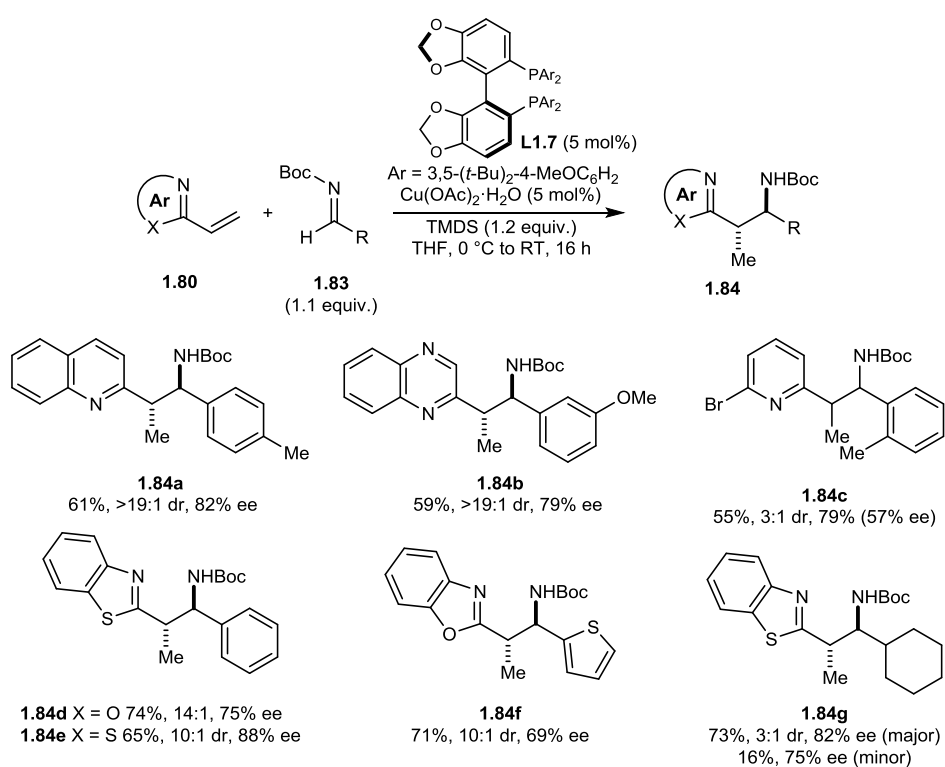




Scheme 1.45: Reductive coupling of alkenylazaarenes **1.80** with ketones **1.67**.^[47]

Further investigation by the same group with regards to π -electrophiles as potential coupling partners for this transformation led to the recently published work on the enantioselective copper-catalysed reductive coupling of vinylazaarenes **1.80** with *N*-Boc protected aldimines **1.83**.^[48] During the extensive studies, they found that in the presence of (*S*)-DTBM-SEGPHOS bisphosphine ligand **L1.7** (5 mol%), 1,1,3,3-tetramethyldisiloxane (TMDS, 1.2 equivalents), the reaction proceeded smoothly in THF at room temperature to give reductive coupling products **1.84** as the *anti*-diastereomer, opposite to that observed by the Krische group^[46] (Scheme 1.46). Pleasingly, the reaction worked for a broad range of vinylazaarenes such as quinolines **1.84a**, pyrimidines **1.84b**, pyridines **1.84c**, benzothiazoles **1.84d**, **1.84e**, **1.84g** and benzoxazoles **1.84f**. In terms of the tested *N*-Boc protected aldimines, various substituents were tolerated at different positions on the phenyl ring. Furthermore, imines containing a heteroaryl moiety like thienyl, were also successful **1.84f**.





Scheme 1.46: Reductive coupling of vinylazaarenes **1.80** with *N*-Boc imines **1.83**.^[48]



1.2 CONCLUSIONS

To summarise, it has been shown that azaarenes are important molecules that can provide complex products in an enantio- and diastereoselective fashion. Alkenylazaarenes can act as electrophiles due to the electron-withdrawing C=N moieties embedded in their structures, and provide Michael addition products with excellent stereoselectivity. In addition, alkylazaarenes may act as nucleophiles once activated, and can be then trapped with various π -electrophiles to release interesting molecules.

In the Results and Discussion section, studies regarding 2-alkylazaarenes as pronucleophiles in addition reactions to *N*-Boc imines and nitroalkenes catalysed by a chiral Pd(II)-bisoxazoline complex will be described. Prior to this work, no enantioselective variant of this reaction was known. Furthermore, the final product can be functionalised further to give a wide range of chiral amines, which are important substructures in various natural products, pharmaceuticals and industrial products.

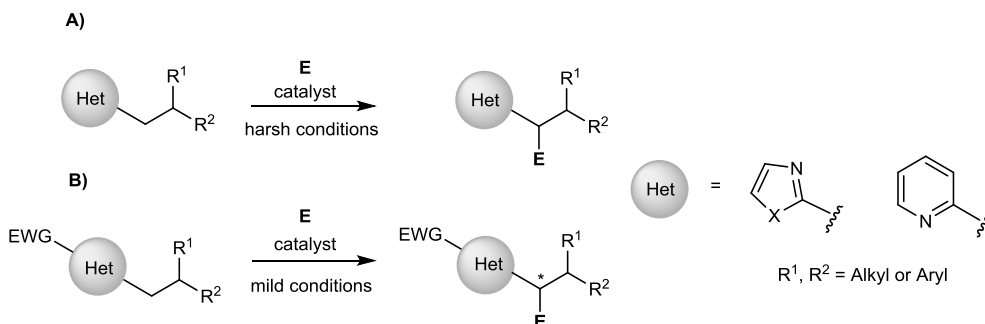


1.3 RESULTS AND DISCUSSION

Unless stated otherwise conversions and diastereomeric ratio were determined by ^1H NMR analysis of the unpurified reaction mixtures. Yields are of pure isolated products. Enantiomeric excesses of the major diastereomer determined by chiral HPLC analysis.

1.3.1 CATALYTIC SOFT ENOLISATION OF HETEROARENES FOR ASYMMETRIC C–C BOND FORMATION

The first part of the introduction provides information regarding synthetic strategies which enable functionalisation of alkylazaarenes *via* C–H deprotonation. As the acidity of the methylene group of alkylazaarenes is low, (e.g. for 2-benzylpyridine $pK_a = 28.2$ in DMSO), harsh conditions such as long reaction times, the addition of an external base or high temperatures are often required to achieve reasonable yields (Scheme 1.47A). Most of the literature precedent covers racemic examples of the nucleophilic additions of alkylazaarenes to imines or nitroalkenes and to the best of our knowledge; an enantioselective variant has not yet been reported. At this stage, we considered whether having an electron-withdrawing group attached to a heterocycle would help to acidify the α -proton, allowing milder and thus more suitable conditions for asymmetric catalysis (Scheme 1.47B).



Scheme 1.47: Azaaromatics as substrates in Mannich-type reactions.

1.3.2 SYNTHESIS OF 2-ALKYLSUBSTITUTED AZAARENES

The synthesis of 2-alkylazaarenes is straightforward. In general, commercially available amino-alcohols and amino-thiols were condensed with orthoesters to give various benzo- and benzothiozoles **1.85** (Table 1.1).



Table 1.1: Synthesis of benzoxazoles and benzothiazoles.^[43]

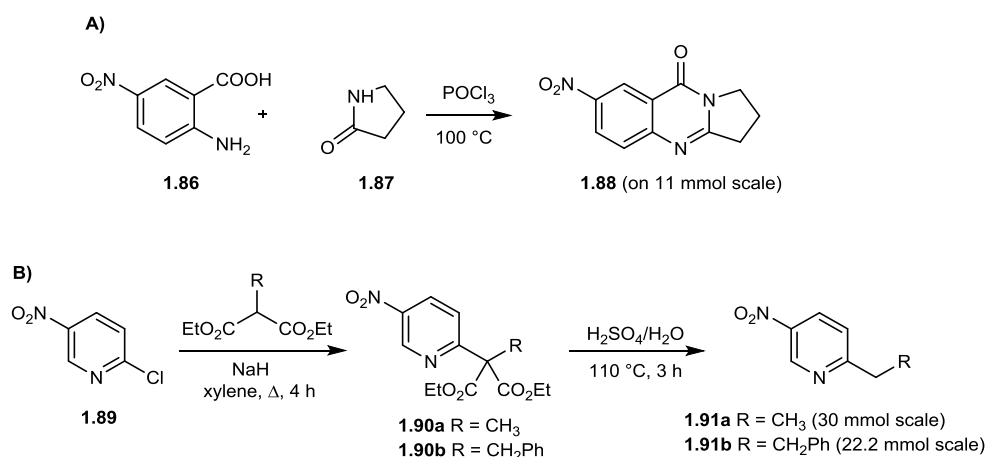
<p> $R^1 = \text{NO}_2, \text{CO}_2\text{Me}, \text{CN}$ $X = \text{O}, \text{S}$ </p> <p> $R^2 = \text{Me}, \text{Et}$ $R^3 = \text{Me}, \text{Et}, n\text{-Pr}, n\text{-Bu}$ $R^4 = \text{CH}_2\text{OMe}$ </p>			
Entry	Product		Yield (%)
1		1.85a	90 ^a
2		1.85b	44 ^a
3		1.85c	93 ^b
4		1.85d	89 ^c
5		1.85e	91 ^d
6		1.85f	96 ^e
7		1.85g	94 ^e
8		1.85h	94 ^e
9		1.85i	42 ^f
10		1.85j	25 ^g
11		1.85k	97 ^h

Reactions conducted on a: ^a32 mmol scale, ^b12 mmol, ^c16 mmol, ^d2.16 mmol, ^e3.00 mmol, ^f36.8 mmol, ^g5.00 mmol, ^h10 mmol.

An alternative approach was used for obtaining pyrroloquinazolinone **1.88** by coupling 2-amino-5-nitrobenzoic acid **1.86** with 2-pyrrolidinone **1.87** (Scheme



1.48A) in the presence of POCl_3 . Also, 3-nitropyridines **1.91** were synthesised by the nucleophilic aromatic substitution of chloropyridine **1.89** with ethyl malonates **1.90** followed by hydrolysis and decarboxylation (Scheme 1.48B).

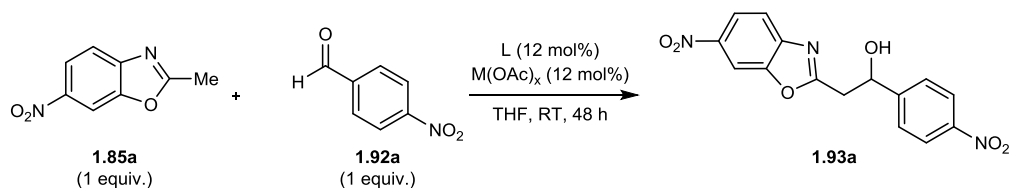


Scheme 1.48: Synthesis of various alkylazaarenes.

1.3.3 SCREENING OF VARIOUS ELECTROPHILES

The reaction between commercially available 2-methyl-6-nitrobenzoxazole **1.85a** and *p*-nitrobenzaldehyde **1.92a** was chosen for catalyst development. Screening of various acetate sources, used as bases in this case to deprotonate the α -proton in **1.85a**, revealed that the combination of AgOAc (12 mol%) and *rac*-BINAP (12 mol%) was the most efficient catalytic system, while other Lewis acids gave either lower conversion or the desired product was not observed (Table 1.2, entries 1–6). A control experiment showed that no reaction occurred in the presence of the Lewis acid only. Changing the ligand for 2,2'-BiPy was less effective at room temperature (Table 1.2, entry 7) and heating the reaction to 100 °C did not significantly improve conversion (~45%). Furthermore, switching from THF to 1,4-dioxane and carrying out reaction at room temperature, 60 °C and 100 °C gave **1.93a** in 16%, 11% and 30% conversion, respectively. Other metal acetates such as In(III) , Pd(II) , Ni(II) , Cu(I) , Cu(II) were not effective (Table 1.2, entries 8–12).



Table 1.2: Screening of reaction conditions.

Entry	$M(OAc)_x$	Ligand	Solvent	Conversion (%)
1	AgOAc	<i>rac</i> -BINAP	THF	60
2	CuOAc	<i>rac</i> -BINAP	THF	10
3	Cu(OAc) ₂	<i>rac</i> -BINAP	THF	33
4	In(OAc) ₃	<i>rac</i> -BINAP	THF	<5
5	Pd(OAc) ₂	<i>rac</i> -BINAP	THF	<5
6	Ni(OAc) ₂	<i>rac</i> -BINAP	THF	<5
7	AgOAc	2,2'-BiPy	THF	42
8	CuOAc	2,2'-BiPy	THF	<5
9	Cu(OAc) ₂	2,2'-BiPy	THF	<5
10	In(OAc) ₃	2,2'-BiPy	THF	<5
11	Pd(OAc) ₂	2,2'-BiPy	THF	7
12	Ni(OAc) ₂	2,2'-BiPy	THF	6

To broaden the reaction scope, a range of heterocycles **1.85** and **1.88** were reacted with *p*-nitrobenzaldehyde **1.92a** (Table 1.3). The combination of *rac*-BINAP with AgOAc in THF was, in most cases, a good catalytic system. The highest conversion was observed for heterocycles **1.93b**, **1.93l–n**, which were obtained in 73%, 72%, 66% and 56%, respectively (Table 1.3, entries 1–4); heterocycles **1.85o–r**, gave the desired product in low conversion between 26 and 40% (compounds **1.93o–r**). The product **1.94a** derived from the heterocycle **1.88** was identified by NMR analysis; however the reaction mixture was too complex to determine an accurate conversion.



Table 1.3: Screening of various heterocycles.^a

$\text{Ar}-\text{N}=\text{C}(\text{X})-\text{CH}_2-\text{R} + \text{H}-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{NO}_2 \xrightarrow[\text{THF, RT, 48 h}]{\text{AgOAc (12 mol\%), } \text{rac-BINAP (12 mol\%)}}$

1.85 or 1.88 (1 equiv.) **1.92a** (1 equiv.) **1.93 or 1.94**

Entry	Heterocycle	Product	Conversion (%)
1	 1.85b	 1.93b	73
2	 1.85l	 1.93l	72
3	 1.85m	 1.93m	66
4	 1.85n	 1.93n	56
5	 1.85o	 1.93o	40
6	 1.85p	 1.93p	35
7	 1.85r	 1.93r	26
8	 1.88	 1.94a	ND

^aUnless stated otherwise conversions were determined by ¹H NMR analysis of the unpurified reaction mixture, ND – not determined

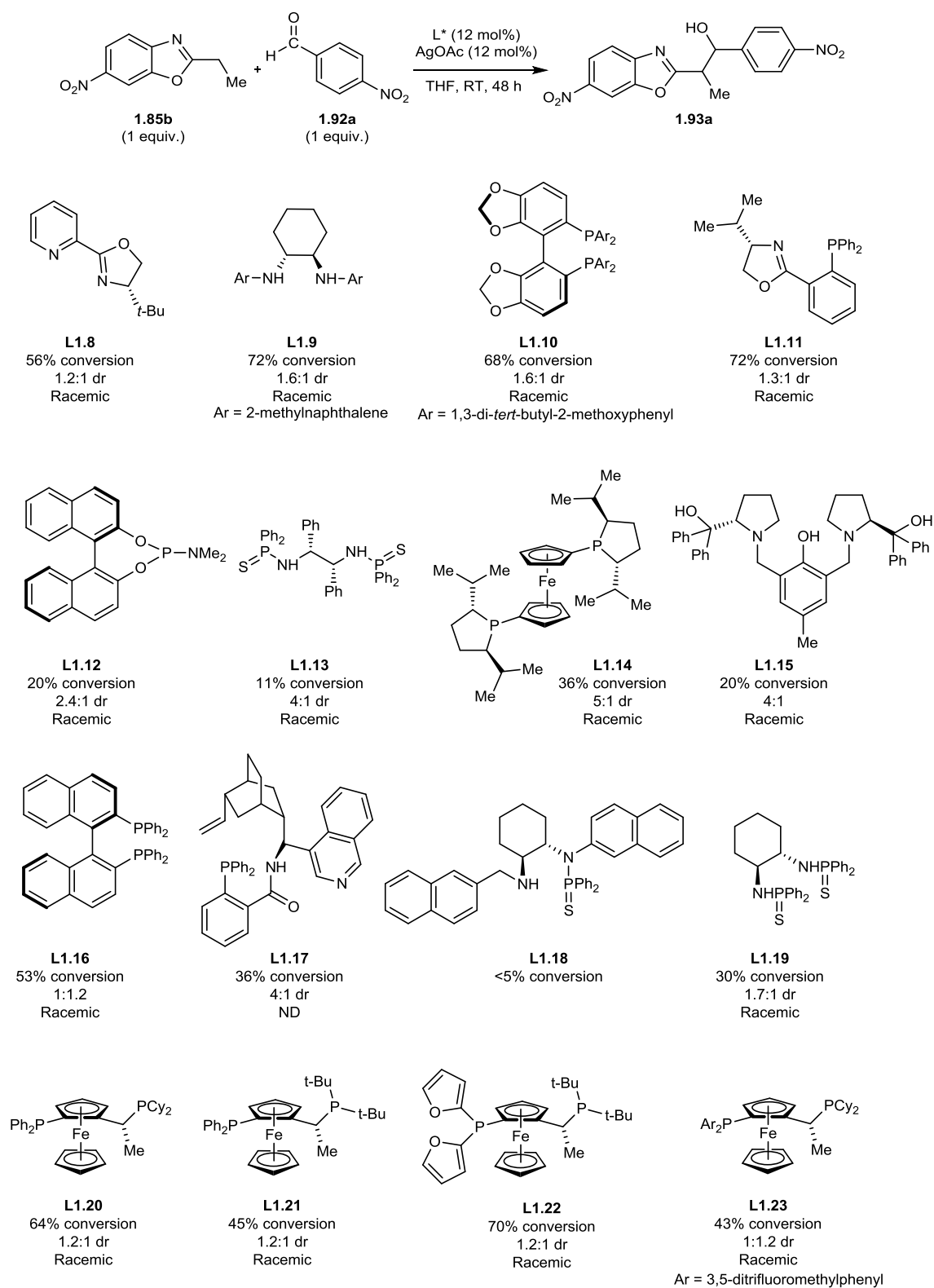
Although the aforementioned heterocycles were not providing generally good yields for the addition products, we decided to investigate if the nucleophilic addition reaction of alkylazarenes with aldehydes could proceed in a stereoselective fashion.

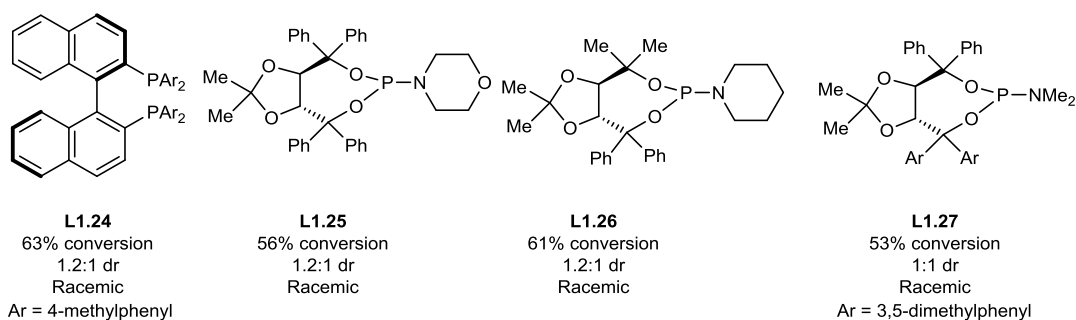


A variety of chiral ligands were evaluated in the model reaction of 2-ethyl-6-nitro-1,3-benzoxazole **1.85b** and *p*-nitrobenzaldehyde **1.92a**. Unfortunately, the addition product **1.93a** was obtained as a racemate and with low diastereoselectivity ranging from a 1:1 to a 4.9:1 ratio (Table 1.4).

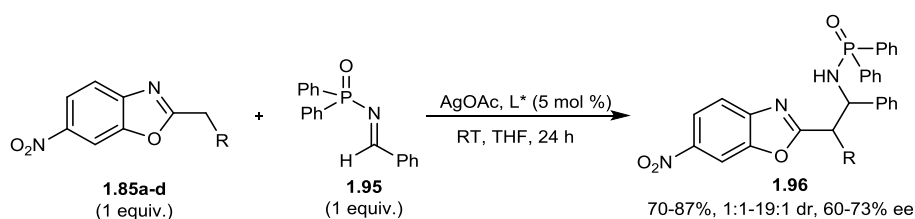


Table 1.4: Evaluation of chiral ligands.





In light of these results, our new strategy was to test different classes of π -electrophiles which might provide the addition product in good yields and enantioselectivity. Contemporaneously, within our group the reaction of *N*-DPP-imine **1.95** and various benzoxazoles **1.85a–d** was being investigated (Scheme 1.49). In the presence of AgOAc and various chiral ligands, a number of alkylheteroarenes were explored. Unfortunately, conditions giving both high ee's and dr's could not be found.

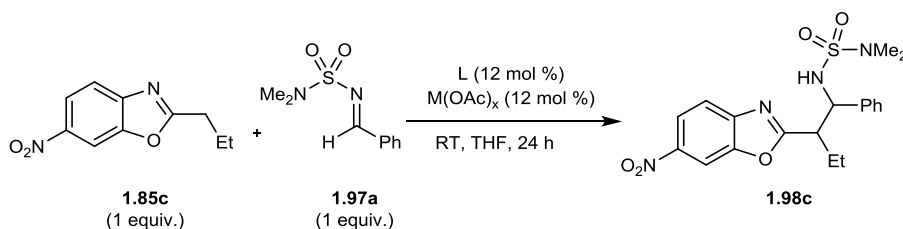


Scheme 1.49: Nucleophilic additions of azaarenes **1.85** to *N*-DPP imine **1.95**.

Although *N*-DPP imines showed some promise, they were not giving consistent results, so our efforts were directed towards other classes of imines.

Our investigation started with screening sulfamoyl-imine **1.97** against 6-nitro-2-propyl-1,3-benzoxazole **1.85c** (Table 1.5). This study identified AgOAc (12 mol%) and *rac*-BINAP (12 mol%) in THF at room temperature to be the most suitable reaction conditions (Table 1.5, entry 1) giving the desired racemic product in 70% conversion. The [AgOAc/2,2'-BiPy/THF] catalytic system was also effective but lower conversion was observed (Table 1.5, entry 2). Unfortunately, no improvement was obtained when various Lewis acids were tested, such as CuOAc, Cu(OAc)₂, Pd(OAc)₂ (Table 1.5, entries 3–5).



Table 1.5: Scope of racemic reaction.

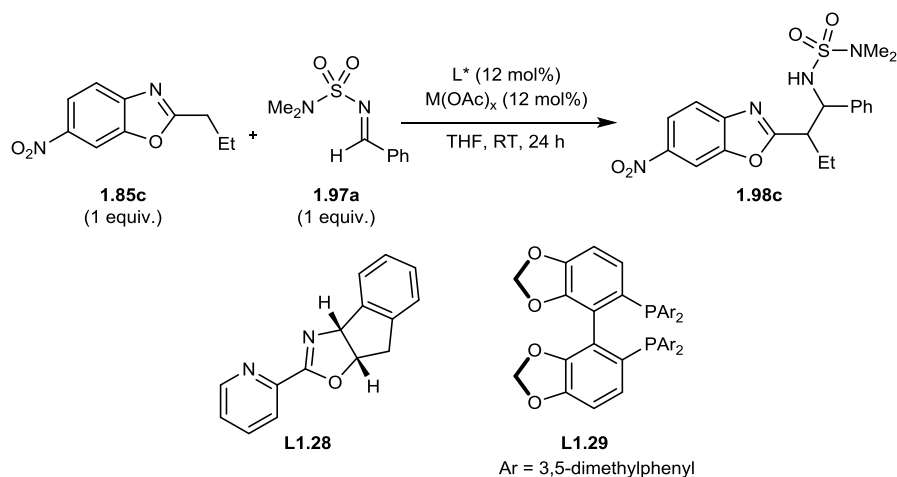
Entry	M(OAc) _x	Ligand	Conversion (%)	dr (%)
1	AgOAc	<i>rac</i> -BINAP	70	2.7:1
2	AgOAc	2,2'-BiPy	51	2.7:1
3	CuOAc	<i>rac</i> -BINAP	<5	ND
4	Cu(OAc) ₂	<i>rac</i> -BINAP	<5	ND
5	Pd(OAc) ₂	2,2'-BiPy	20	6.7:1

ND – not determined

To develop an asymmetric version of this reaction, next, various co-catalysts AgOAc, Pd(OAc)₂, CuOAc and Cu(OAc)₂ were screened along with a variety of chiral ligands (Table 1.6). A very encouraging result 64%, 94% ee, >19:1 dr (Table 1.6 entry 13) was obtained using 12 mol% Pd(OAc)₂ and (*S*)-DM-SEGPHOS **L1.29** in THF at room temperature. Running the reaction on 0.5 mM scale conversion reached up to 80%. A solvent screen at room temperature indicated that changing THF for DME gave a comparable outcome (63%, 91% ee) but a decrease in dr was observed (9:1), (Table 1.7 entry 2). Higher conversion was generally observed with a AgOAc catalyst, but the ee was <50% with various ligands and the dr was highly variable (Table 1.6, entries 1–2, 5–6). CuOAc and Cu(OAc)₂ in combination with (*S*)-DM-SEGPHOS **L1.29** gave similar results, both giving 40–50% conversion but low enantiomeric excess between 15–20%, however a complete reversal of dr was observed in both cases (Table 1.6 entries 25–26).



Table 1.6: Ligand optimisation.



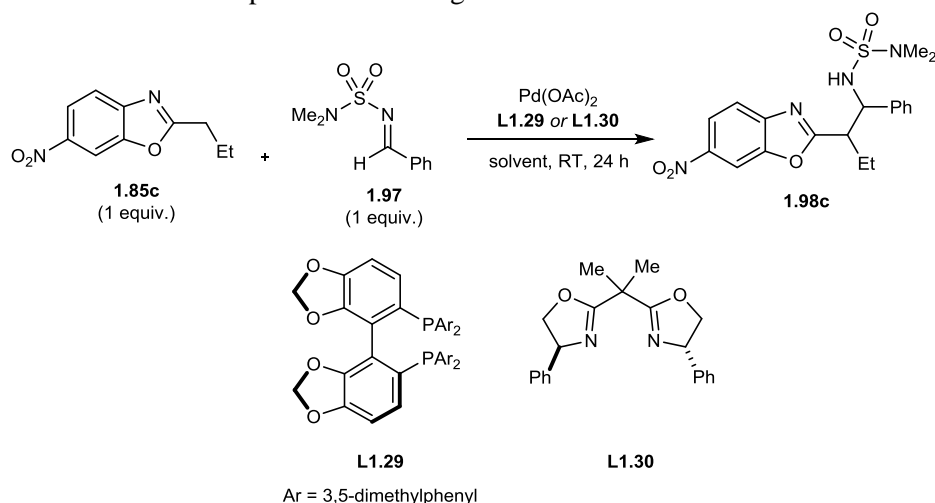
Entry	$M(OAc)_x$	Ligand	Conversion (%)	dr (%)	ee (%)
1	AgOAc	L1.28	86	1.4:1	40(3)
2	AgOAc	L1.9	74	1.4:1	19(13)
3	$Pd(OAc)_2$	L1.28	35	2.3:1	11(37)
4	$Pd(OAc)_2$	L1.9	47	7.3:1	13(3)
5	AgOAc	L1.20	76	1.7:1	10(10)
6	AgOAc	L1.10	43	4.8:1	40(0)
7	$Pd(OAc)_2$	L1.20	18	7.3:1	3(20)
8	$Pd(OAc)_2$	L1.10	<5	ND	ND
9	AgOAc	L1.15	<5	ND	ND
10	AgOAc	L1.29	76	3.2:1	47(7)
11	AgOAc	L1.16	65	2.2:1	23(0)
12	$Pd(OAc)_2$	L1.15	<5	ND	ND
13	$Pd(OAc)_2$	L1.29	64	>19:1	94
14	$Pd(OAc)_2$	L1.16	21	>19:1	63
15	AgOAc	L1.8	80	1.3:1	ND
16	AgOAc	L1.13	<5	ND	ND
17	AgOAc	L1.18	<5	ND	ND
18	AgOAc	L1.19	<5	ND	ND
19	$Pd(OAc)_2$	L1.8	60	4.5:1	20(65)
20	$Pd(OAc)_2$	L1.13	<5	ND	ND
21	$Pd(OAc)_2$	L1.18	<5	ND	ND
22	$Pd(OAc)_2$	L1.19	<5	ND	ND
23	CuOAc	L1.29	51	1:5.6	19(13)
24	$Cu(OAc)_2$	L1.29	38	1:5.6	23(17)

ND – not determined; (-)-ee of the minor diastereoisomer



In an attempt to simultaneously lower the catalyst loading and increase conversion, a solvent screen at higher temperature was also conducted (Table 1.7). This screen indicated that elevated temperatures resulted in a significant decrease in ee, though high ee could be still obtained at 60 °C in DCE (91% ee), although use of DCE led to a decrease in conversion (Table 1.7 entry 7). Unfortunately, an increase to a higher temperature (100 °C) revealed thermal instability of the catalyst (Table 1.7, entries 8–9). As part of an ongoing ligand screen, application of the Ph-DM-Box ligand **L1.30** in combination with Pd(OAc)₂ gave the addition product **1.98c** in conversion greater than 90%, 14:1 dr and 89% ee (Table 1.7, entry 10). This result provided our best combination of conversion and stereoselectivity to date.

Table 1.7: Solvent and temperature screening.

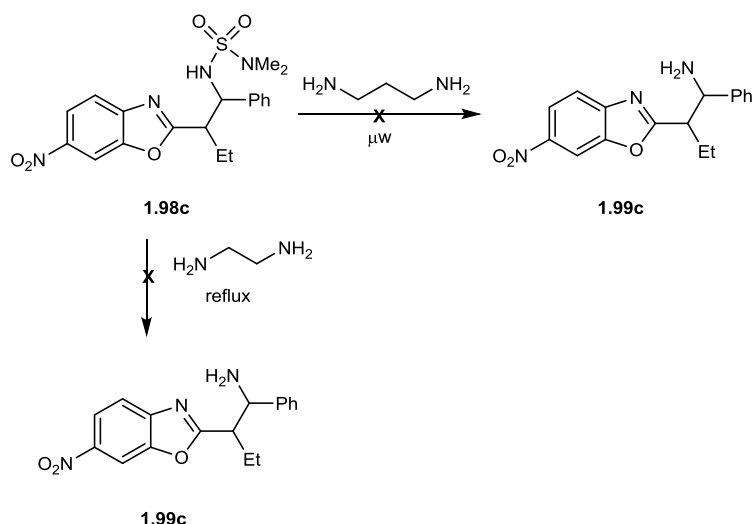


Entry	Ligand	Solvent	Temperature (°C)	Catalyst (mol%)	Conversion (%)	dr	ee (%)
1	L1.29	THF	RT	12	64	>19:1	94
2	L1.29	DME	RT	12	63	9:1	91
3	L1.29	DCE	RT	12	<5	-	-
4	L1.29	THF	60	5	39	9:1	67
5	L1.29	DME	60	5	26	9:1	ND
6	L1.29	toluene	60	5	43	9:1	77
7	L1.29	DCE	60	5	59	9:1	91
8	L1.29	dioxane	100	5	<5	-	-
9	L1.29	DCE	100	5	<5	-	-
10	L1.30	THF	RT	10	>90	14:1	86

ND – not determined



At this stage, deprotection of the product was investigated to establish the potential synthetic utility of this process. According to literature procedures,^{[49], [50]} the treatment of sulfamoyl-protected amine product **1.98c** with diamines at reflux or under microwave irradiation should cleave the sulfamoyl group giving the desired free amine **1.99c** (Scheme 1.50). Unfortunately, none of the applied methods gave the desired product, instead complex mixtures were obtained, even at room temperature. According to literature precedent,^[51] it is highly likely that the reduction of the aromatic nitro group may occur under these conditions which would explain the failure of this transformation. Attempts to cleave the sulfamoyl group with HCl (6 M) led to slow hydrolysis of the benzoxazole to the corresponding amide, and no detectible sulfamoyl hydrolysis. This deprotection problem was not investigated any further and it was decided to change our strategy slightly.



Scheme 1.50: Attempts of deprotection of product **1.98c**.

In light of the results obtained, alternative imines were reconsidered in our studies (Figure 1.2). We were interested in coupling the alkylazaarenes with imines that have a cleavable protecting group. For instance, we excluded *N*-tosyl imine **1.100** as the protecting group in the product would be difficult to cleave and thus the products would have very little synthetic utility. *N*-Nosyl-imine **1.101** proved to have very low reactivity under a variety of conditions and pyridylsulfonyl-imine **1.102** showed only low conversion in the presence of some AgOAc catalysts. Unfortunately, addition to



these imines was not observed in the presence of $\text{Pd}(\text{OAc})_2$, CuOAc or $\text{Cu}(\text{OAc})_2$ catalysts.

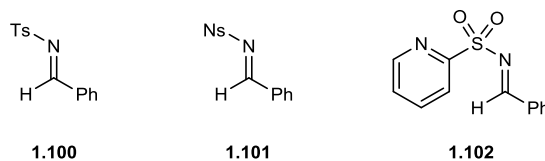


Figure 1.2: Various *N*-protected imines used for the nucleophilic addition reactions with alkylazaarenes.

1.3.4 *N*-BOC PROTECTED IMINES AS ELECTROPHILES IN NUCLEOPHILIC ADDITION REACTIONS

Next, our efforts were focused on *N*-Boc-protected imines. The deprotection of the product is facile, making *N*-Boc imines very attractive electrophiles. The synthesis of the protected imines is well documented in the literature, whereby formation of sulfonyl carbamates **1.103** is followed by treatment with base to give *N*-Boc imines **1.83** (Table 1.8).



Table 1.8: The general synthesis of *N*-Boc imines.^a

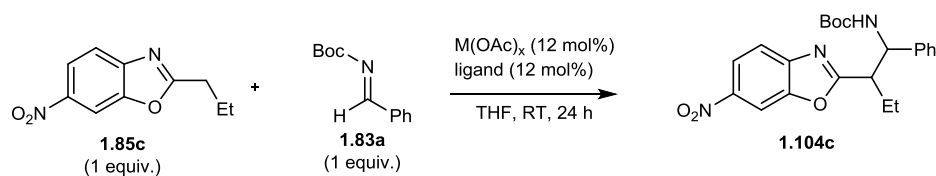
Sulfonylcarbamate		Yield (%)	Imines		Yield (%)
	1.103a	98 ^[52]		1.83a	95
	1.103b	79 ^[53]		1.83b	80
	1.103c	71 ^[54]		1.83c	93
	1.103d	43 ^[52]		1.83d	91
	1.103e	83 ^[55]		1.83e	87
	1.103f	78 ^[43]		1.83f	92
	1.103g	76 ^[52]		1.83g	93
	1.103h	70 ^[43]		1.83h	89
	1.103i	53 ^[43]		1.83i	54

N-Boc imines proved to be very suitable electrophiles for the addition of 2-alkylazaarenes. As shown below in Table 1.9, 6-nitro-2-propyl-1,3-benzoxazole **1.85c** and *N*-Boc imine **1.83a** were screened in combination with various ligands and metal acetates at room temperature. The best result was obtained when AgOAc and



rac-BINAP in THF were applied, giving the corresponding adduct **1.104c** in 80% conversion (Table 1.9, entry 3). CuOAc, Cu(OAc)₂ and Pd(OAc)₂ in combination with dppe or 2,2'-BiPy ligands were not effective for this reaction.

Table 1.9: Reaction conditions for the model reaction.

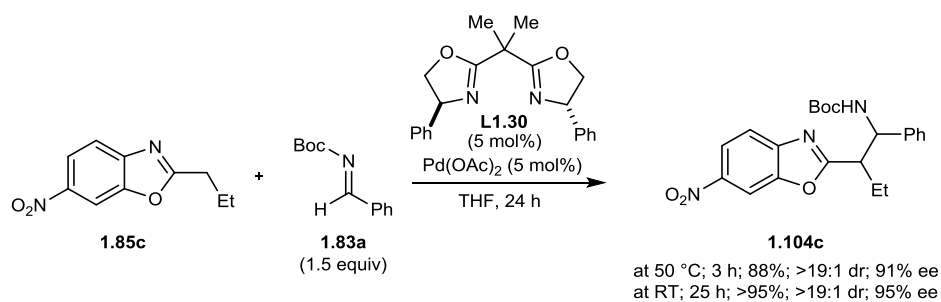


Entry	$M(OAc)_x$	Ligand	Conversion[%]
1	CuOAc	<i>rac</i> -BINAP	<5
2	Cu(OAc) ₂	<i>rac</i> -BINAP	<5
3	AgOAc	<i>rac</i> -BINAP	80
4	Pd(OAc) ₂	<i>rac</i> -BINAP	<5
5	CuOAc	Dppe	30
6	Cu(OAc) ₂	Dppe	26
7	AgOAc	Dppe	<5
8	Pd(OAc) ₂	Dppe	<5
9	CuOAc	2,2'-BiPy	<5
10	Cu(OAc) ₂	2,2'-BiPy	<5
11	AgOAc	2,2'-Bipy	<5

^aUnless stated otherwise conversions were determined by ¹H NMR analysis of the unpurified reaction mixture

With these results, our focus turned to the development of an enantioselective version of this reaction. A particularly active catalyst [Pd(OAc)₂, Ph-DM-Box **L1.30**] effective in the studies with sulfamoyl-imines before, was used in the reaction of propylbenzoxazole **1.85c** with phenyl *N*-Boc imine **1.83a** to give chiral amine **1.104c**. Pleasingly, high conversion, ee and dr were observed at room temperature, and largely conserved at 50 °C, a temperature which allowed a much shorter reaction time (Scheme 1.51).

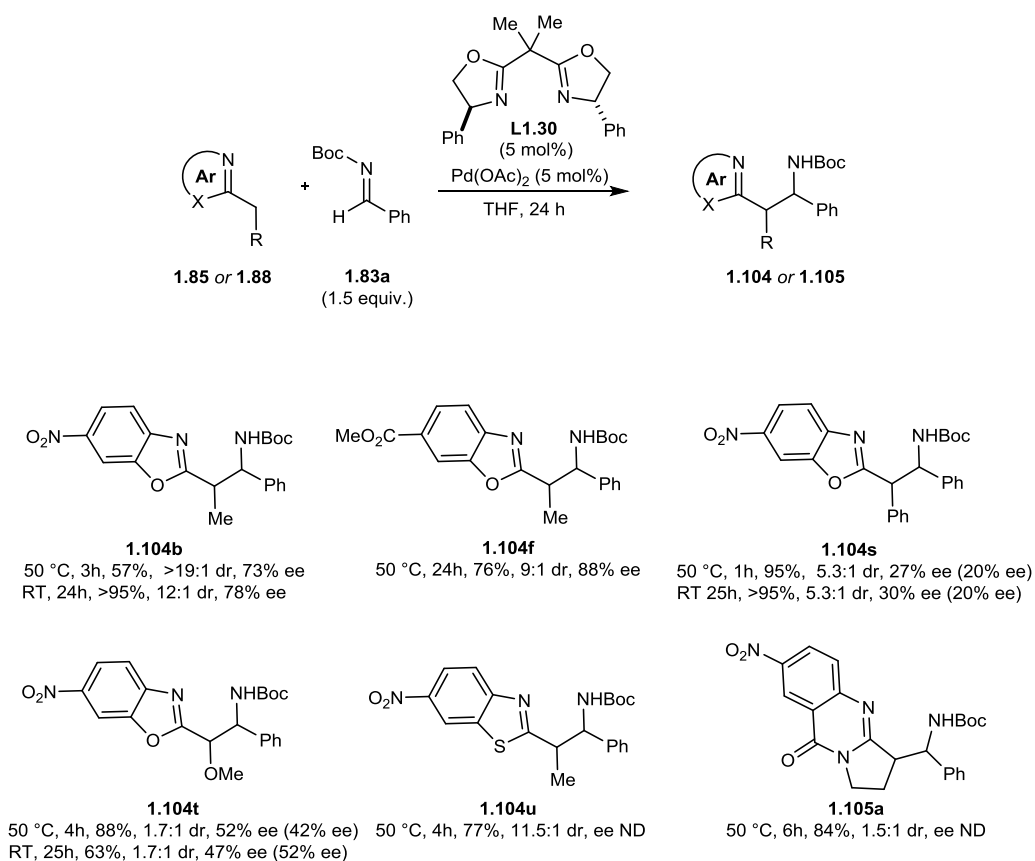




Scheme 1.51: Addition reaction of azaarene **1.85c** to *N*-Boc imine **1.83a**.

The optimised reaction conditions were applied to other heterocyclic substrates, **1.85** and **1.88** to assess the substrate scope of the nucleophilic addition process (Scheme 1.52). Disappointingly, these conditions did not appear to be very general. For instance, whilst the benzoxazole addition products **1.104s** or **1.104t** were obtained with high yields, the enantio- and diastereoselectivity was low to moderate. Heating at 50 °C shortened the reaction time and improved the yield but stereoselectivity was still poor.

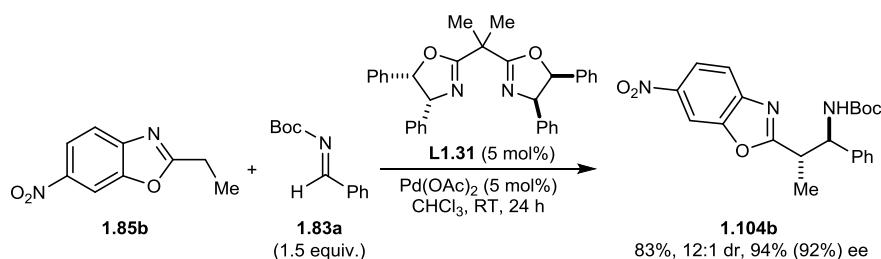




Scheme 1.52: Screening of various heterocycles with *N*-Boc protected imine **1.83a**.

In light of these results, our efforts were focused on synthesising more sterically bulky version of ligand **L1.30** to see if the stereoselectivity could be improved. A tetraphenylbis(oxazoline) TPDM-Box ligand **L1.31** was investigated. Pleasingly, the reaction of 2-ethyl-benzoxazole **1.85b** with *N*-Boc imine **1.83a** in the presence of the chiral complex composed of 5 mol% Pd(OAc)₂ and a TPDM-Box ligand **L1.31** delivered the final product **1.104b** in a great yield and enantioselectivity (Scheme 1.53). Based on these results a range of 2-alkylazaarenes was next investigated.





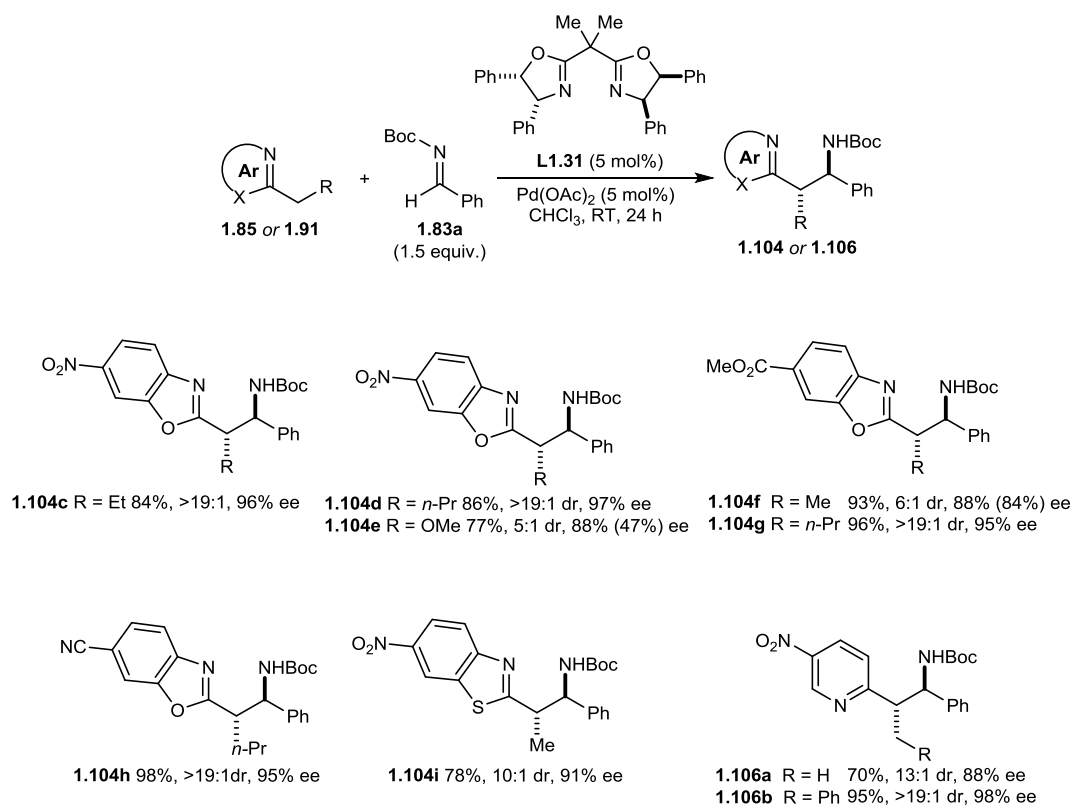
Scheme 1.53: Nucleophilic addition of 2-ethyl-benzoxazole **1.85b** to *N*-Boc imine **1.83a**.

1.3.5 SUBSTRATE SCOPE

2-Alkylazaarenes

Application of the optimised conditions in the reaction of various azaarenes with phenyl *N*-Boc-protected imine **1.83a** gave the addition products in excellent yields, good to high enantio- and diastereoselectivity (Scheme 1.54). 2-Alkyl-6-nitrobenzoxazoles **1.85c** and **1.85d** containing an ethyl or *n*-propyl substituent at the α -position were tolerated and delivered the addition products in high yield, enantio- and diastereoselectivity at room temperature. (Scheme 1.54, compounds **1.104c** and **1.104d**). With respect to 2-methoxy-6-nitrobenzoxazole **1.85e**, the reaction proceeded smoothly but gave only a 5:1 mixture of diastereoisomers (product **1.104e**). Unfortunately, 2-methyl-6-nitrobenzoxazole **1.85a** did not give the expected product but double substitution was observed instead. Changing the nitro group at the 6-position of alkylazaarene for either an ester or cyano group required heating the reaction at 50 °C due to the lower reactivity of the starting materials (products **1.104f–h**). Enantio- and diastereoselectivity was, in these cases, still high in comparison to the corresponding reactions carried out at room temperature. This process is also applicable to other azaarenes such as 6-nitrobenzothiazole **1.85i**, which gave the addition product **1.104i** in 78% yield, 10:1 dr and 99% ee, as well as for 3-nitropyridines where the products (**1.106a** and **b**) were obtained in high yield and great diastereo- and enantiodiscrimination.

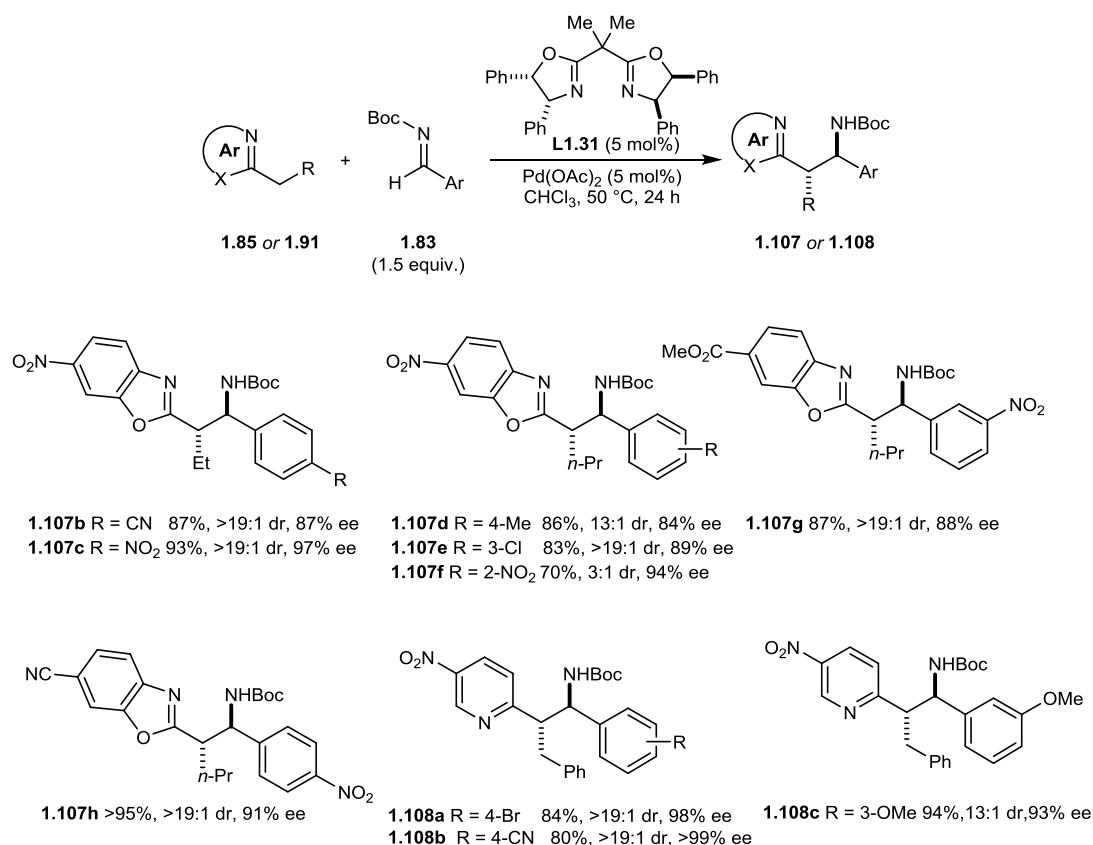




Scheme 1.54: Enantioselective Pd-catalysed addition of various 2-alkylazaarenes to phenyl *N*-Boc imine **1.83a**.

In order to broaden the reaction scope, we focused on various aromatic *N*-Boc-protected aldimines **1.83** (Scheme 1.55). Aromatic imines with substituents at the *para* and the *meta* positions at the phenyl ring (such as methyl, bromo, chloro, nitro, cyano or methoxy) underwent the addition reaction successfully with a range of different 2-alkylazaarenes in high yield, enantio- and diastereoselection. These reaction conditions were also applied to an *ortho* substituted aromatic imine and gave the expected product in high yield and enantioselectivity but with moderate diastereoselectivity which is believed to be due to steric hindrance (product **1.107f**).



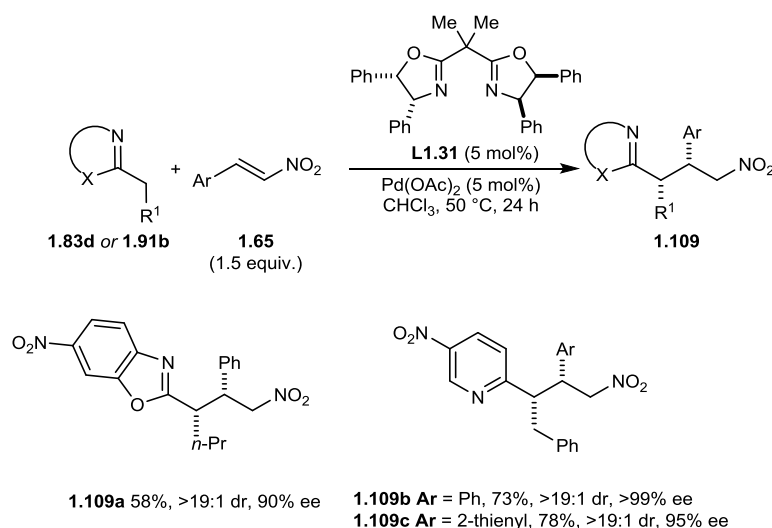


Scheme 1.55: Enantioselective Pd-catalysed additions of alkylazaarenes to various *N*-Boc imines.

Nitroalkenes

Having assessed the scope of *N*-Boc-protected imines tolerated in the Pd-catalysed nucleophilic addition reactions of alkylazaarenes, we next investigated alternative π -electrophiles to further expand this process. Pleasingly, it was found that this process was not only limited to aromatic *N*-Boc imines; nitroalkenes were also effective coupling partners under identical conditions. As demonstrated, substrates **1.85d** and **1.91b**, gave the addition products as a single diastereoisomer with high enantiodiscrimination and good yield (Scheme 1.56).



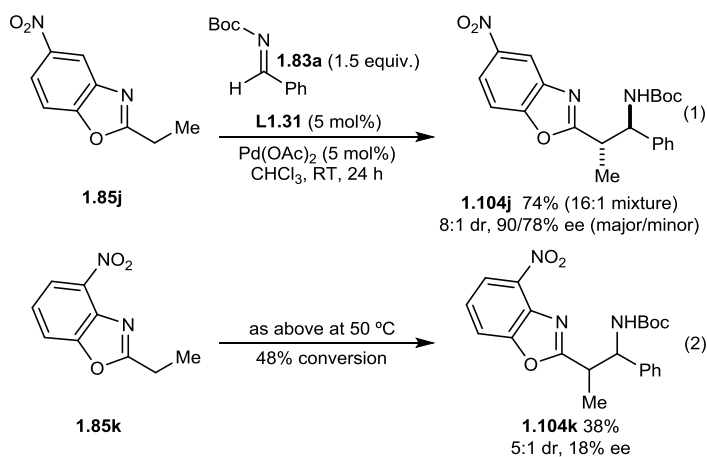


Scheme 1.56: Enantioselective Pd-catalysed additions to nitroalkenes.

1.3.6 THE ROLE OF THE ELECTRON-WITHDRAWING GROUP IN THE AZAARENE

After having generated a range of chiral, protected amines with high molecular and stereochemical complexity, we decided to investigate the importance of the position of the electron-withdrawing group at the azaarene. It was decided to prepare 2-ethyl-5-nitrobenzoxazole **1.85j** in which the nitro group is not conjugated to the developing negative charge on deprotonation. The reaction of **1.85j** with phenyl-*N*-Boc imine **1.83a** was conducted under previously optimised conditions. Despite the lack of conjugation, the coupled product **1.104j** (Scheme 1.57, entry 1) was obtained as a 16:1 inseparable mixture of diastereoisomers in 74% yield, with enantiomeric excess of 90% and 78% for the major and minor diastereomers, respectively. Interestingly, since the stabilisation of the conjugate base of **1.85j** by the mesomeric effect is not possible in this case, it suggests that the inductive effect of the nitro group is sufficient for the reaction to proceed. This shows the possibility of broadening the reaction scope for substrates bearing an electron-withdrawing group at the 5-position. Conducting the reaction with conjugated nitro derivative 2-ethyl-4-nitrobenzoxazole **1.85k**, gave the final product **1.104k** in poor yield and diastereoselectivity. This result may possibly be explained by the coordination of the nitro group to the metal centre of the palladium catalyst.

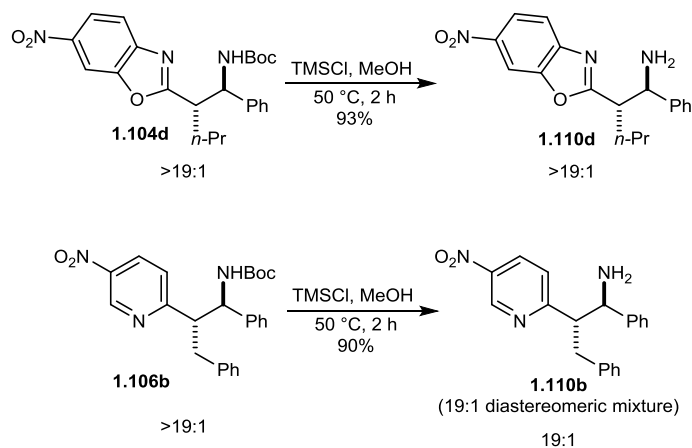




Scheme 1.57: Variation of an electron-withdrawing group on azaarene.

1.3.7 MANIPULATION OF THE PRODUCT VIA DEPROTECTION OF *N*-BOC GROUP

Ideally for this new enantioselective methodology for the alkylation of *N*-Boc imines to be a useful synthetic approach, the nitrogen protecting group should be readily cleaved. Removal of the *N*-Boc protecting group was conducted by generating dilute HCl *in situ* from TMSCl in methanol. This allowed the formation of the free chiral amine product under relatively mild conditions (Scheme 1.58). The products **1.110d** and **1.110b** were obtained in 90% and 93% yield respectively, with a very small erosion of diastereoselectivity in the latter case.

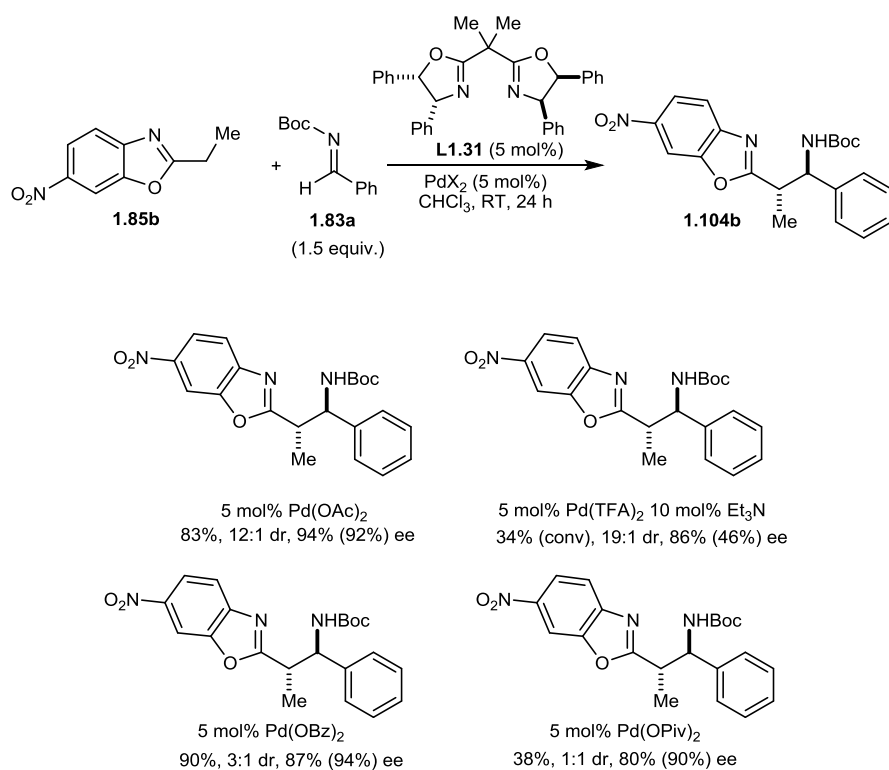


Scheme 1.58: Deprotection of the final products.



1.3.8 THE ROLE OF THE COUNTERION ON THE REACTION OUTCOME

We also explored if any of other carboxylate counterions can be used as alternatives to metal acetates. The general reaction between 2-ethyl-6-nitrobenzoxazole **1.85b** and phenyl *N*-Boc imine **1.83a** was run under standard conditions but with Pd(TFA)₂ in place of Pd(OAc)₂ (Scheme 1.59). However, not even a trace of product was obtained. With an addition of 10 mol% Et₃N, the conversion reached only 34%. As trifluoroacetates are less basic than acetate anions the addition of an external base was needed. Then, an analogous experiment was conducted using Pd(OBz)₂, which gave the addition product in 90% yield, 3:1 dr and 87% (97%) ee (major/minor). Finally, changing the anion by using Pd(OPiv)₂ gave the desired product in only 38% yield. It is believed that benzoate and pivalate anions are more bulky than acetate which may explain low stereoselectivity observed. These results conclude that both the basicity and the size of the counterion are crucial for the reaction outcome.

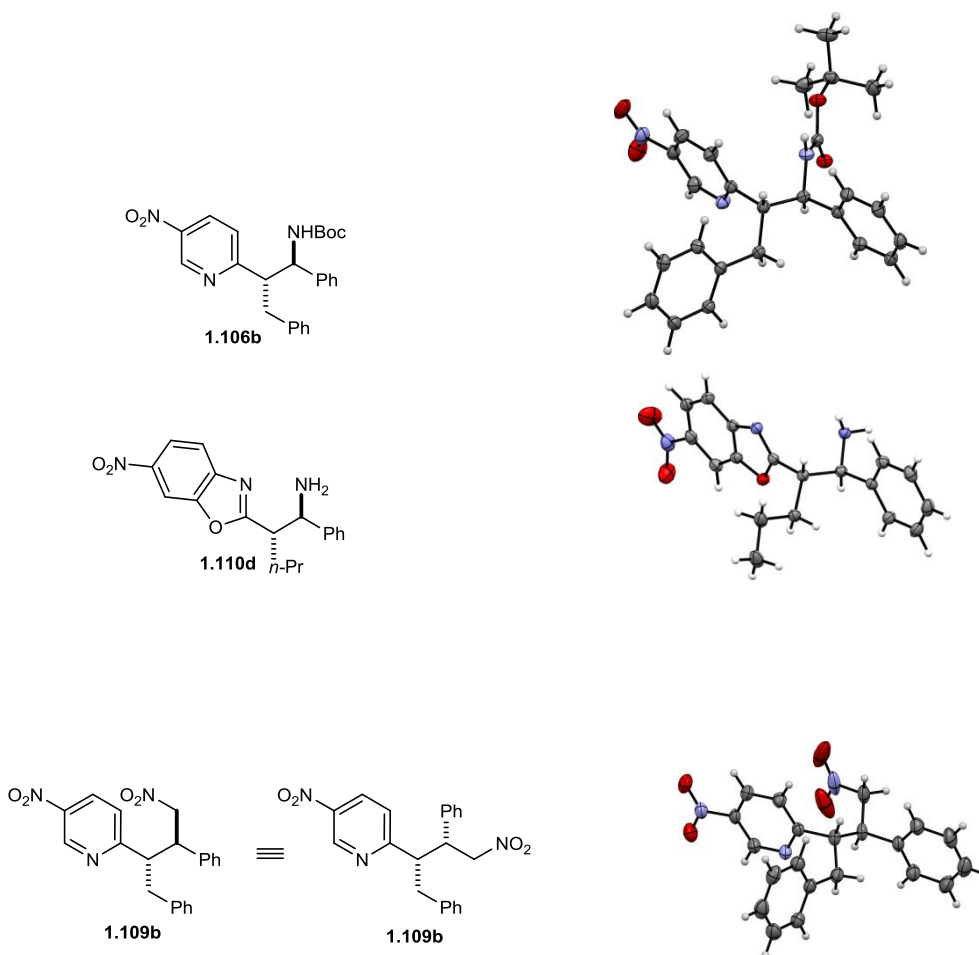


Scheme 1.59: The role of various counterions on the reaction outcome.



1.3.9 X-RAY ANALYSIS AND STEREOCHEMICAL MODEL

The relative and absolute stereochemistries of the addition products **1.106b**, **1.110d**, and **1.109b** were determined by X-ray crystallography using a copper radiation source. The stereochemistries of the remaining products were assigned by analogy (Scheme 1.60)

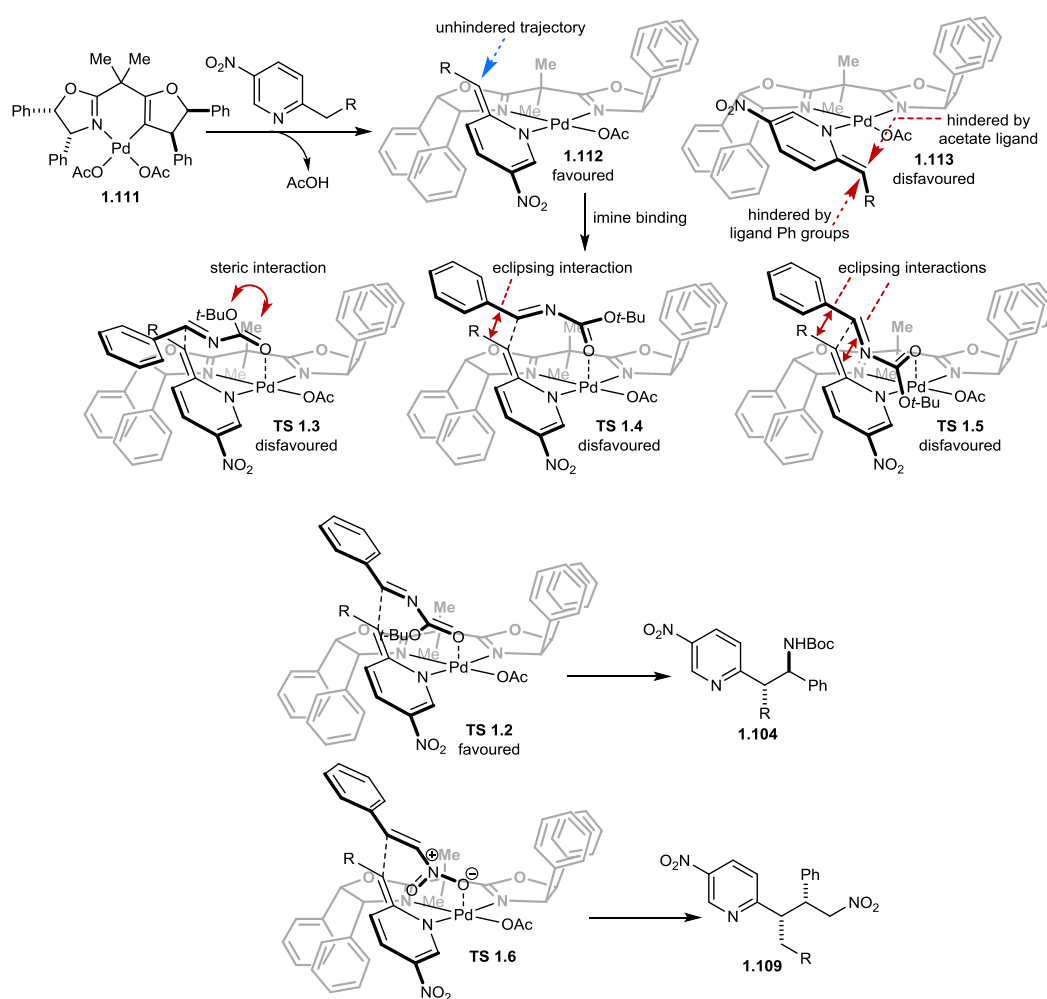


Scheme 1.60: Crystal structures of compounds **1.106b**, **1.110d**, **1.109b**.

Based on these results, a stereochemical model was proposed (Scheme 1.61) First, the deprotonation of an alkylazaarene by an acetate anion from the palladium complex **1.111** occurs, giving the Pd-bound azaallyl species **1.112**. In this case the *E*-stereochemistry has been adopted in order to minimise the steric interactions between the *R*-substituent and the other ligand. The imine approach is more likely to happen in this conformation as the top face is relatively unhindered. However, if the azaallyl ligand adopts an alternative conformation like in species **1.113**, the imine



coordination/binding is disfavoured as the top face is hindered by the acetate ligand while the bottom face is blocked by the phenyl groups of the chiral complex. The formation of four distinct transition states from conformation **1.112** is plausible. In **TS 1.4** and **TS 1.5** the imine possesses an *s-cis* geometry which is unfavourable due to eclipsing interactions. However, in the case of the more favourable staggered conformations **TS 1.2** and **TS 1.3**, where an imine adopts *s-trans* geometry, the latter is disfavoured as the *tert*-butyl group of the imine clashes with one of the methyl groups of the chiral ligand. Therefore, the reaction is believed to go through **TS 1.2**. A similar approach can be applied to the stereochemical outcome of the nitroalkene addition, through **TS 1.6**.

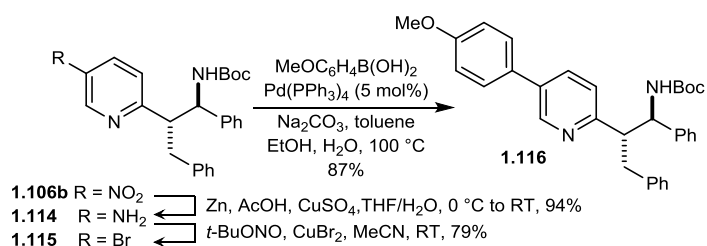


Scheme 1.61: Proposed stereochemical model



1.3.10 ELABORATION OF AN ADDUCT

Finally, to further demonstrate the utility of our method we applied our conditions to the synthesis of a more complex biaryl adduct (Scheme 1.62). First, the reduction of the aromatic nitro group to an amine was achieved in the presence of metallic zinc, CuSO₄ and acetic acid giving product **1.114** in 94% yield. Then, the conversion of this amine into brominated product **1.115** was achieved *via* the Sandmeyer reaction, followed by a Suzuki-Miyaura coupling with 4-methoxyphenylboronic acid to produce the final product **1.116** in 80% yield.

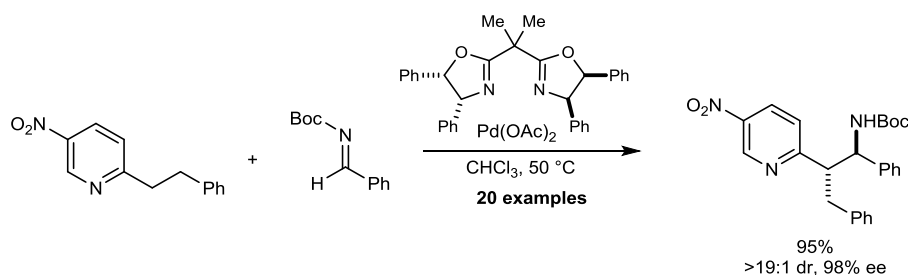


Scheme 1.62: Further transformations of the addition product **1.106b**.



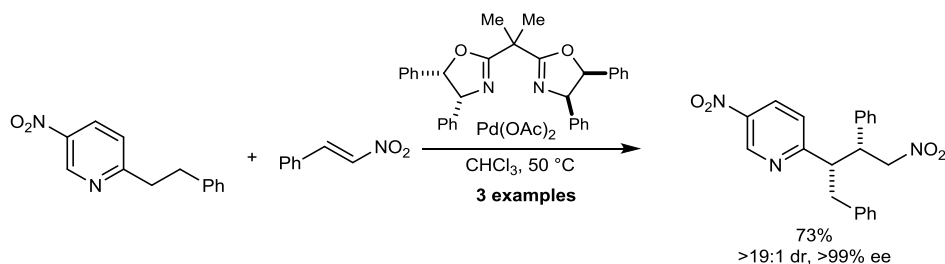
1.4 CONCLUSIONS AND FUTURE WORK

We have reported the palladium-catalysed enantioselective addition of alkylazaarenes to *N*-Boc imines using a bis(oxazoline) ligand to attain excellent enantioselectivities, diastereomeric ratios, and yields. These reaction proceed under mild conditions with no external base, no inert atmosphere and often ambient temperatures. The electron-withdrawing substituent on the heterocycle was found to be essential to modulate the pKa sufficiently to allow the chiral palladium enolate to form.



Scheme 1.63: Diastereo- and enantioselective Pd-catalysed additions of 2-alkylazaarenes to *N*-Boc imines and nitroalkenes.

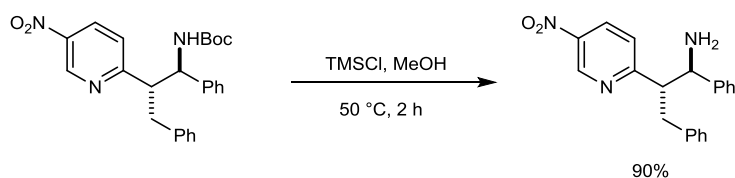
We then extended this work to encompass nitroalkenes as the π -acceptors and demonstrates the the palladium enolate could undergo Michael addition with similar excellent results indicating that this process works for both 1,2- and 1,4-addition reactions.



Scheme 1.64: Diastereo- and enantioselective Pd-catalysed additions of 2-alkylazaarenes to nitroalkenes

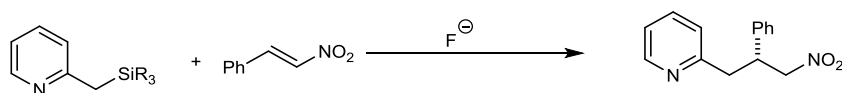
Finally, the judicious choice of using *N*-Boc imines as the Mannich acceptors allowed the facile removal of the protecting group to enable the rapid synthesis of the corresponding chiral free amine.





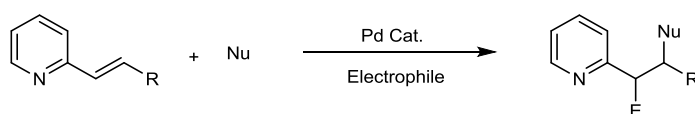
Scheme 1.65: The deprotection of the product to give amine products

Our efforts to extend this work are currently directed towards the investigation of α -TMS-protected alkylazaarenes and their ability to act as nucleophiles in conjugate addition reactions with π -electrophiles. We believe that the formation of an enolate by desilylation rather than deprotonation of an alkylazaarene could be possible and the formation of a strong Si-X bond ($X = \text{O}, \text{F}$) would provide a thermodynamic driving force for this reaction. Also by using this method of activation, it may be possible to not require a strong electron-withdrawing group on the alkylazaarene.



Scheme 1.66: Proposed activation of α -silyl heterocycles

Previously we have reported alkenylazaarenes to be excellent latent nucleophiles, conjugate addition of a hydride using copper catalysis formed a copper-enolate which could then undergo highly enantioselective aldol^[47] and Mannich^[48] reactions to generate molecular complexity. We believe that similar palladium catalysed domino processes could be feasible to allow the generation of multiple stereocentres in one step.



Scheme 1.67: Domino trapping of palladium enolates



1.5 EXPERIMENTAL

This project was done in the collaboration with one of my work colleagues Dr Daniel Best. The data presented in this section represents experiments performed by me in regards to this project.

General Information

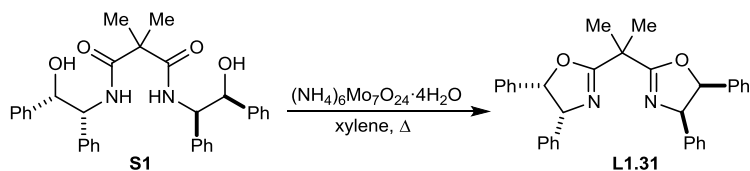
THF and CH₂Cl₂ were dried and purified by passage through activated alumina columns using a solvent purification system. All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F₂₅₄ 0.2 mm precoated plates. Product spots were visualised by UV light at 254 nm, and subsequently developed using vanillin, potassium permanganate, or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35-70 micron) employing the step gradient elution in the mobile phase stated. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Shimadzu IRAffinity-1 instrument as a thin film on sodium chloride plates or as a dilute solution in CHCl₃. ¹H NMR spectra were recorded on a Bruker AV500 (500 MHz), a Bruker AVA400 (400 MHz) spectrometer, or a Bruker OPEN400 (400 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as an internal standard (CDCl₃ at 7.27 ppm, CD₃OD at 3.31 ppm, (CD₃)₂SO at 2.50 ppm). Abbreviations used in the description of resonances are: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ¹³C NMR spectra were recorded on a Bruker AV500 (125.8 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as an internal standard (CDCl₃ at 77.0 ppm, CD₃OD at 49.0 ppm, (CD₃)₂SO at 39.5 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High-resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer or a Finnigan MAT 95XP spectrometer at the EPSRC National Mass Spectrometry Service Centre,



Swansea University, or on a Finnigan MAT 900 XLT spectrometer at the School of Chemistry, University of Edinburgh. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter with a path length of 1 dm. Chiral HPLC analysis was performed on an Agilent 1260 instrument using 4.6 x 250 mm columns. Authentic racemic samples of products for chiral HPLC assay determinations were obtained using *rac*-BINAP/AgOAc as the catalyst in THF, or *rac*-2,2-bis[2-(4-phenyl-1,3-oxazolinyl)]propane/Pd(OAc)₂ as the catalyst in CHCl₃ or THF.

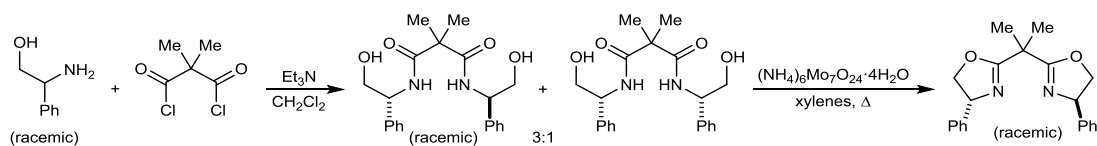
Preparation of Ligands

2,2-Bis[(4*R*,5*S*)-4,5-diphenyl-1,3-oxazolin-2-yl]propane (**L1.31**)^[56]



Following a modified literature procedure,^[57] a suspension of the diamide **S1** (558 mg, 1.07 mmol) and (NH₄)₆Mo₇O₂₄·4H₂O (190 mg, 0.154 mmol, 100 mol% Mo) in xylenes (50 mL) was heated at reflux using a Dean-Stark apparatus for 24 h. TLC analysis (40% acetone/hexane) revealed complete consumption of the diamide (*R_f* 0.30) and the formation of a major product (*R_f* 0.60). The reaction mixture was pre-adsorbed onto silica gel and purified by column chromatography (5→20% acetone/hexane) to provide the bis(oxazoline) ligand **L1.31** (418 mg, 80%) as a white crystalline solid. Physical and spectral properties were in accordance with those reported in the literature.^[57]

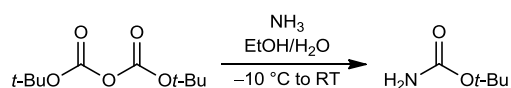
Rac-2,2-Bis[(4-phenyl-1,3-oxazolin-2-yl)]propane



DL-Phenylglycinol (440 mg, 3.21 mmol) was reacted with dimethylmalonyl chloride (0.20 mL, 1.54 mmol) in the presence of Et₃N (0.64 mL, 4.63 mmol) in CH₂Cl₂ (10 mL) by the method previously described^[56] to give *N,N'*-bis[2-(2-hydroxy-1-phenylethyl)]propanediamide (502 mg, 88%) as an inseparable 3:1 mixture of isomers. The crude mixed diamides (502 mg, 1.35 mmol) and (NH₄)₆Mo₇O₂₄·4H₂O (85 mg, 0.69 mmol, 35 mol% Mo) were suspended in xylenes (40 mL) and the mixture was stirred at reflux using a Dean-Stark apparatus for 4 h. TLC analysis (25% acetone/hexane) revealed complete consumption of the diamides (R_f 0.00) and formation of a major product (R_f 0.20). The reaction mixture was pre-adsorbed onto silica gel and purified column chromatography (2→18% acetone/hexane) to separate the major component (colourless oil, 249 mg, 55%) from the mixture. NMR data for the racemic ligand were identical to those previously reported for enantiopure 2,2-bis[2-(4(*S*)-phenyl-1,3-oxazolinyl)]propane.^[58]

Preparation of *N*-Boc Imines

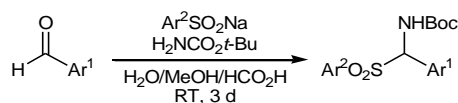
tert-Butyl carbamate



To a solution of di-*tert*-butyl dicarbonate (50.9 g, 233 mmol) in EtOH (500 mL) at –10 °C was added 35% NH₃ (aq) (50 mL) over 5 min. The reaction mixture was stirred vigorously for a further 30 min at –10 °C to 0 °C, and then at room temperature for 18 h. The solvents were removed from the resulting thick suspension *in vacuo* at 50 °C to ensure decomposition of ammonium *tert*-butyl carbonate. The residue was suspended in hexane (500 mL), stirred at 60 °C for 1 h, and then recrystallised from refluxing hexane (total volume ~650 mL) to provide *tert*-butyl carbamate (25.9 g, 95%) as a white crystalline solid. Physical and spectral properties were in accordance with those reported in the literature.^[59]

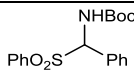
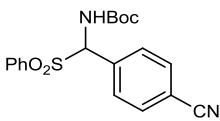
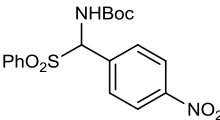
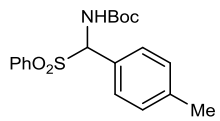
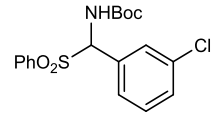
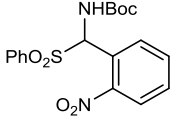
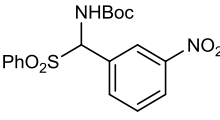
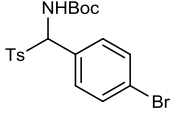
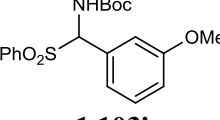


***tert*-Butyl *N*-[(benzenesulfonyl)(phenyl)methyl]carbamates and *tert*-butyl *N*-{[(4-methylbenzene)sulfonyl](phenyl)methyl}carbamates**

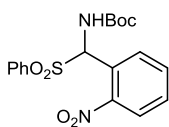


Following a slightly modified literature procedure,^[52] the appropriate aldehyde (15 mmol) was suspended in 2:1:0.7 H₂O/MeOH/HCO₂H (40 mL) and stirred until the mixture became homogeneous. Gentle heating was necessary to achieve complete dissolution in most cases, and addition of additional solvent was required where noted. Sodium benzenesulfinate (20 mmol) or sodium 4-methylbenzenesulfinate (20 mmol) and *tert*-butyl carbamate (10 mmol) were then added sequentially. The reaction mixture was stirred for 3 d, the solids collected by filtration and triturated with H₂O and then the organic solvent/mixture specified to leave the sulfonylcarbamate.



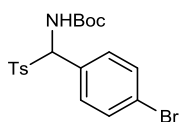
Sulfonylcarbamate	Additional Solvent	Trituration Solvents	Yield (%)	Previously characterised
 1.103a	—	hexane	98	Yes ^[52]
 1.103b	—	1:1 Et ₂ O/hexane	79	Yes ^[53]
 1.103c	—	3:5 hexane/CH ₂ Cl ₂	71	Yes ^[54]
 1.103d	—	5:3 hexane/toluene	43	Yes ^[52]
 1.103e	—	10:1 hexane/CH ₂ Cl ₂	83	Yes ^[55]
 1.103f	—	1:1 Et ₂ O/hexane	78	No
 1.103g	MeOH (10mL)	3:5 hexane/ CH ₂ Cl ₂	76	Yes ^[52]
 1.103h	MeOH (10mL)	1:1 Et ₂ O/hexane; toluene	70	No
 1.103i	—	1:1 Et ₂ O/hexane then 5:3 hexane/toluene	53	No





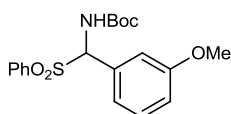
***tert*-Butyl *N*-[(benzenesulfonyl)(2-nitrophenyl)methyl]carbamate
1.103f.**

m.p. 168-170 °C; IR (film) 3138, 1697 (C=O), 1526 (NO₂), 1346 (NO₂), 1150, 1084, 1011, 687, 586 cm⁻¹; ¹H NMR (500 MHz, (CD₃)₂SO at 70 °C*) δ 8.65 (1H, br s, NH), 8.09 (2H, t, *J* = 8.9 Hz, ArH), 7.84 (1H, t, *J* = 7.8 Hz, ArH), 7.81-7.65 (6H, m, ArH), 7.21 (1H, d, *J* = 10.7 Hz, CHN), 1.22 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂SO at 70 °C) δ 148.8 (C), 136.4 (C), 134.0 (CH), 133.1 (CH), 130.5 (CH), 130.5 (CH), 129.1 (2 x CH), 128.6 (C), 128.4 (2 x CH), 124.6 (CH), 124.0 (C), 79.6 (C), 68.7 (CH), 27.4 (3 x CH₃). *A rotameric mixture was observed at room temperature.



***tert*-Butyl *N*-[(4-bromophenyl)[(4-methylbenzene)sulfonyl]
methyl] 1.103h**

m.p. 180-182 °C; IR (film) 2961, 1694 (C=O), 1503, 1487, 1304 (SO₂), 1247, 1140 (SO₂), 1085, 713, 640 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.78 (2H, d, *J* = 8.0 Hz, ArH), 7.57-7.52 (2H, m, ArH), 7.34 (2H, d, *J* = 8.0 Hz, ArH), 7.32 (2H, d, *J* = 8.5 Hz, ArH), 5.86 (1H, d, *J* = 10.4 Hz, CHN), 5.75 (1H, d, *J* = 10.4 Hz, NH), 2.44 (3H, s, ArCH₃), 1.27 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 153.4 (C), 145.3 (C), 131.9 (2 x CH), 130.4 (2 x CH), 129.8 (2 x CH), 129.5 (2 x CH), 129.1 (C), 124.9 (C), 124.3 (C), 81.3 (C), 73.2 (CH), 27.9 (3 x CH₃), 21.6 (CH₃).



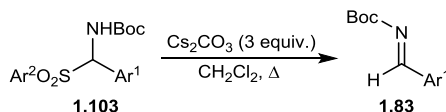
***tert*-Butyl *N*-[(benzenesulfonyl)(3-methoxyphenyl)methyl]
carbamate 1.103i.**

m.p. 140-142 °C; IR (film) 2959, 1697 (C=O), 1585, 1504, 1312 (SO₂), 1286, 1246, 1145 (SO₂), 1082, 716, 689 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.92 (2H, d, *J* = 7.5 Hz, ArH), 7.65 (1H, t, *J* = 7.4 Hz, ArH), 7.54 (2H, d, *J* = 7.7 Hz, ArH), 7.33 (1H, d, *J* = 8.1 Hz, ArH), 7.03 (1H, d, *J* = 7.5 Hz, ArH), 7.00-6.94 (2H, m, ArH), 5.90 (1H, d, *J* = 10.5 Hz, CHN), 5.79 (1H, d, *J* = 10.5 Hz, NH), 3.81 (3H, s, OCH₃), 1.27 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 159.7 (C), 153.4 (C), 136.9 (C), 133.9 (CH), 131.3 (C), 129.8 (2 x CH), 129.4 (CH), 129.0 (2 x CH),



121.1 (CH), 115.6 (CH), 114.5 (CH), 81.2 (C), 73.9 (CH), 55.3 (CH₃), 28.0 (3 x CH₃).

***N*-Boc Imines**

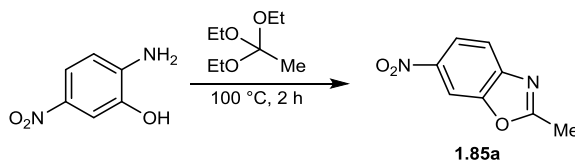


A suspension of flame-dried Cs₂CO₃ (6.0 mmol) in a solution of the appropriate sulfonylcarbamate (2.0 mmol) in dry, alcohol-free CH₂Cl₂ (40 mL) was heated at reflux. Small aliquots were removed periodically, filtered, and analysed by ¹H NMR spectroscopy (using CDCl₃ treated with K₂CO₃ to remove trace HCl which hydrolyzes the *N*-Boc imine) to confirm completion of the reaction (1–4 h). The reaction mixture was cooled to room temperature, diluted with hexane (40 mL), stirred for 10 min, and filtered. The filtrate was concentrated *in vacuo* at <20 °C to leave the *N*-Boc imine (90–100%). Data for imines **1.83a** Ar = Ph,^[52] **1.83b** Ar = *p*-NCC₆H₄,^[54] **1.83c** Ar = *p*-O₂NC₆H₄,^[55] **1.83d** Ar = *p*-MeC₆H₄,^[52] **1.83e** Ar = *m*-ClC₆H₄,^[60] **1.83f** Ar = *o*-O₂NC₆H₄,^[61] **1.83g** Ar = *m*-O₂NC₆H₄,^[52] **1.83h** Ar = *p*-BrC₆H₄,^[54] and **1.83i** Ar = *m*-MeOC₆H₄,^[62] were in accordance with those reported in the literature.



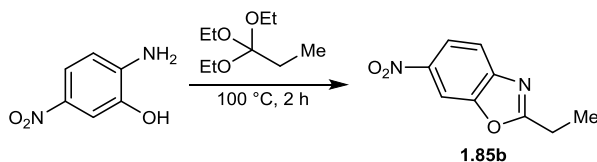
Preparation of Alkylazaarenes

2-Methyl-6-nitro-1,3-benzoxazole (1.85a)^[63]



A mixture of 2-amino-5-nitrophenol (5.0 g, 32 mmol) and triethyl orthoacetate (23.6 mL, 129 mmol) was stirred at 100 °C for 2 hours, cooled to room temperature and the precipitate was collected by filtration and washed with hexane (2 x 25 mL). Purification of the residue by column chromatography (50→80% DCM/hexane) gave the *benzoxazole* **1.85a** (5.22 g, 90%) as a white solid. R_f 0.30 (20% acetone/hexane); m.p. = 150-152 °C; IR (film) 3073, 1614, 1576, 1520 (NO₂), 1463, 1438, 1350 (NO₂), 1269, 1173, 911; ¹H NMR (500 MHz, CDCl₃) δ 8.41 (1H, d, J = 1.8 Hz, ArH); 8.29 (1H, dd, J = 8.7, 2.2 Hz, ArH), 7.76 (1H, dd, J = 8.7 Hz, ArH), 2.74 (3H, s, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 168.8 (C), 150.1 (C), 146.8 (C), 145.0 (C), 120.4 (CH), 119.4 (CH), 106.9 (CH), 14.9 (CH₃). Physical and spectral properties were in accordance with those reported in the literature.^[63]

2-Ethyl-6-nitrobenzoxazole (1.85b)^[64]

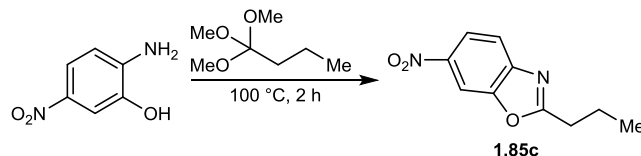


A mixture of 2-amino-5-nitrophenol (5.00 g, 32.0 mmol) and triethyl orthopropionate (7.1 mL, 35 mmol) was stirred at 100 °C for 2 h, cooled to room temperature, and the precipitate was collected by filtration. Recrystallisation of the precipitate (EtOH/water) afforded the *benzoxazole* **1.85b** (2.80 g, 44%) as a pale brown crystalline solid. R_f 0.67 (2% MeOH/DCM); m.p. 82-84 °C; IR (film) 2932, 1569, 1513 (NO₂), 1458, 1420, 1336 (NO₂), 1229, 1151, 1055, 735; ¹H NMR (500 MHz, CDCl₃) δ 8.40 (1H, d, J = 1.9 Hz, ArH), 8.29 (1H, dd, J = 8.7, 2.2 Hz, ArH), 7.77 (1H, d, J = 8.8 Hz, ArH), 3.05 (2H, q, J = 7.6 Hz, CH₂CH₃), 1.50 (3H, t, J = 7.6 Hz,



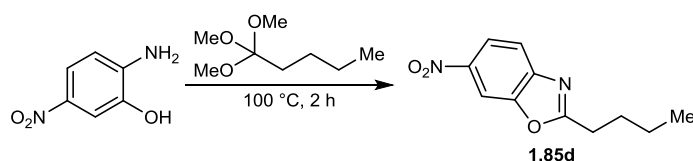
CH₂CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 173.0 (C), 150.0 (C), 146.7 (C), 144.9 (C), 120.3 (CH), 119.4 (CH), 106.9 (CH), 22.4 (CH₂), 10.6 (CH₃). Physical and spectral properties were in accordance with those reported in the literature.^[64]

6-Nitro-2-propylbenzoxazole (1.85c)



A mixture of 2-amino-5-nitrophenol (1.80 g, 12.0 mmol) and trimethyl orthobutyrate (3.9 mL, 24 mmol) was stirred at 100 °C for 2 h, cooled to room temperature, and concentrated *in vacuo*. Purification of the residue by column chromatography (0→3% acetone/toluene) gave the benzoxazole **1.85c** (2.29 g, 93%) as a pale yellow solid. R_f 0.55 (5% acetone/toluene); m.p. 48-50 °C; IR (film) 1570, 1517 (NO₂), 1344 (NO₂), 1234, 1150, 1058, 938, 886, 822, 735 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.40 (1H, d, *J* = 2.1 Hz, ArH), 8.29 (1H, dd, *J* = 8.7, 2.1 Hz, ArH), 7.77 (1H, d, *J* = 8.7 Hz, ArH), 3.00 (2H, t, *J* = 7.5 Hz, CH₂CH₂CH₃), 2.00-1.93 (2H, m, CH₂CH₃), 1.09 (3H, t, *J* = 7.4 Hz, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 172.1 (C), 149.9 (C), 146.7 (C), 144.9 (C), 120.3 (CH), 119.4 (CH), 106.9 (CH), 30.7 (CH₂), 20.0 (CH₂), 13.7 (CH₃); HRMS (ESI +ve) Exact mass calculated for C₁₀H₁₁N₂O₃ [M+H]⁺: 207.0764, found: 207.0763.

2-Butyl-6-nitrobenzoxazole (1.85d)

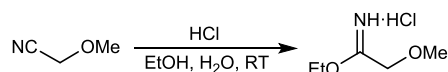


A mixture of 2-amino-5-nitrophenol (2.50 g, 16.0 mmol) and trimethyl orthovalerate (5.8 mL, 33 mmol) was stirred at 100 °C for 2 h, cooled to room temperature, and concentrated *in vacuo*. Purification of the residue by column chromatography (0→3% acetone/toluene) gave the benzoxazole **1.85d** (3.13 g, 89%) as a pale yellow solid. R_f 0.60 (5% acetone/toluene); m.p. 26-28 °C; IR (film) 2960, 2872, 1618, 1568, 1523 (NO₂), 1340 (NO₂), 1265, 1231, 825, 732 cm⁻¹; ¹H NMR (500 MHz,



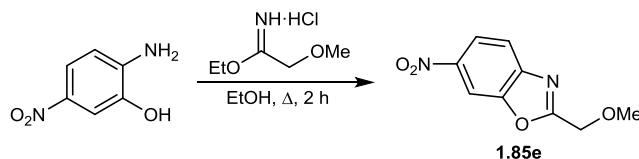
CDCl₃) δ 8.41 (1H, d, J = 2.1 Hz, ArH), 8.30 (1H, dd, J = 8.7, 2.2 Hz, ArH), 7.78 (1H, d, J = 8.7 Hz, ArH), 3.03 (2H, t, J = 7.6 Hz, CH₂CH₂CH₂CH₃), 1.96-1.90 (2H, m, CH₂CH₂CH₃), 1.54-1.46 (2H, m, CH₂CH₃), 1.02 (3H, t, J = 7.4 Hz, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 172.3 (C), 149.9 (C), 146.7 (C), 144.9 (C), 120.3 (CH), 119.4 (CH), 106.9 (CH), 28.5 (2 x CH₂), 22.2 (CH₂), 13.6 (CH₃); HRMS (ESI +ve) Exact mass calculated for C₁₁H₁₃N₂O₃ [M+H]⁺: 221.0921, found: 221.0921.

Ethyl 2-methoxyacetimidate hydrochloride^[65]



To a vigorously stirring mixture of methoxyacetonitrile (1.00 mL, 13.5 mmol) and EtOH (0.85 mL, 14.6 mmol) was added anhydrous HCl (2 M in Et₂O, 7.5 mL, 14 mmol) at RT. After 16 h the precipitate was collected by filtration, washed with Et₂O, and dried *in vacuo* to leave the imidate salt (1.51 g, 73%) as a white solid. Physical and spectral properties were in accordance with those reported in the literature.^[65]

2-Methoxymethyl-6-nitrobenzoxazole (1.85e)

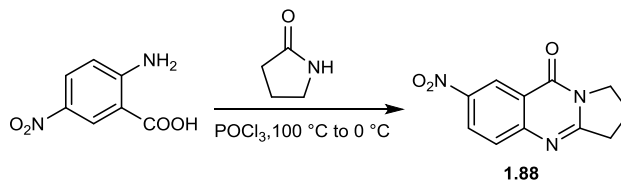


A solution of 2-amino-5-nitrophenol (333 mg, 2.16 mmol) and ethyl 2-methoxyacetimidate hydrochloride (500 mg, 3.28 mmol) in EtOH (2 mL) was stirred at reflux for 2 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (10 mL), washed sequentially with 1:1 brine/saturated aqueous NaHCO₃ solution (2 x 10 mL), and brine (10 mL). The organic layer was dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (0→6% acetone/toluene) gave the *benzoxazole* **1.85e** (411 mg, 91%) as a white crystalline solid. R_f 0.35 (5% acetone/toluene); m.p. 86-88 °C; IR (film) 3097, 2893, 1575, 1517 (NO₂), 1463, 1344 (NO₂), 1139, 1105, 921, 859 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.41 (1H, d, J = 2.2 Hz, ArH), 8.27 (1H, dd, J = 8.8, 2.2 Hz, ArH), 7.80 (1H, d, J = 8.8 Hz, ArH), 4.80 (2H, s, CH₂), 3.55 (3H, s, OCH₃);



^{13}C NMR (125.8 MHz, CDCl_3) δ 167.3 (C), 149.8 (C), 145.9 (C), 145.4 (C), 120.5 (CH), 120.2 (CH), 107.3 (CH), 66.7 (CH_2), 59.5 (CH_3); HRMS (ESI +ve) Exact mass calculated for $\text{C}_9\text{H}_9\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 209.0557, found: 209.0554.

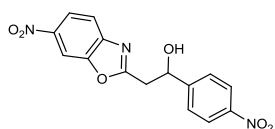
7-Nitro-1*H*,2*H*,3*H*,9*H*-pyrrolo[2,1-*b*]quinazolin-9-one (1.88)



To a mixture of 2-amino-5-nitrobenzoic acid (2.00 g, 11.0 mmol) and 2-pyrrolidinone (1.10 mL, 16.0 mmol), phosphoryl chloride (3.60 mL, 14.0 mmol) was added and the mixture was stirred at 100 °C for 1 h. The reaction mixture was cooled to 0 °C, diluted with water (10 mL), made alkaline with conc. ammonia solution, and extracted with chloroform (3 x 10 mL). The organic layer was collected, dried over MgSO_4 and concentrated *in vacuo*. Purification of the residue by column chromatography (50→80% EtOAc/hexane) gave the *quinazolin-9-one* **1.88** (1.23 g, 47%) as a yellow solid. R_f 0.64 (2% EtOAc/hexane); m.p. 188-190 °C; IR (film) 2927, 1689, 1601, 1569, 1515 (NO_2), 1388 (NO_2), 1331, 1252, 857, 670; ^1H NMR (500 MHz, CDCl_3) δ 9.14 (1H, d, J = 2.6 Hz, ArH), 8.51 (1H, dd, J = 9.0, 2.7 Hz, ArH), 7.7 (1H, d, J = 9.0 Hz, ArH), 4.28-4.25 (2H, m, CH_2), 3.25 (2H, t, J = 8.0 Hz, CH_2), 2.39-2.33 (2H, m, CH_2); ^{13}C NMR (125.8 MHz, CDCl_3) δ 163.2 (C), 159.8 (C), 153.3 (C), 145.3 (C), 128.4 (C), 128.3 (2 x CH), 123.1 (CH), 46.9 (CH_2), 32.9 (CH_2), 19.3 (CH_2).

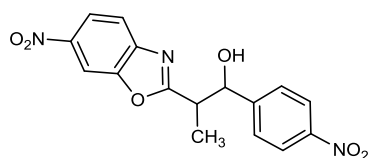


Preparation of racemic products:



2-(6-nitro-1,3-benzoxazole-2-yl)-1-(4-nitrophenyl)ethan-1-ol (**1.93a**).

A mixture of *rac*-BINAP (30.0 mg, 0.05 mmol) and AgOAc (8.00 mg, 0.05 mmol) in THF (2 mL) was stirred at room temperature for 15 min. 1,3-Benzoxazole **1.85a** (71.0 mg, 0.40 mmol) and *p*-nitrobenzaldehyde **1.92a** (46.0 mg, 0.40 mmol) were added and the reaction mixture was stirred at room temperature for 48 h. The mixture was filtered through a short plug of SiO₂, eluted with EtOAc and concentrated *in vacuo*. Purification of the residue by column chromatography (10→80% EtOAc/petroleum ether) gave the addition product **1.93a** as a white crystalline solid (49 mg, 37%). *R*_f 0.39 (40% EtOAc/petroleum ether); m.p. 171-172 °C; IR (film) 1567, 1505 (NO₂), 1340 (NO₂), 1269, 1152, 1063, 851, 869, 679 cm⁻¹; ¹H NMR (400 MHz, (CD₃)₂SO) δ 8.64 (1H, d, *J* = 1.9 Hz, ArH), 8.27 (1H, dd, *J* = 8.8, 2.2 Hz, ArH), 8.23-8.18 (2H, m, ArH), 7.91 (1H, dd, *J* = 6.5, 2.5 Hz, ArH), 7.75-7.70 (2H, m, ArH), 6.10 (1H, d, *J* = 4.8 Hz, OH), 5.37 (1H, app dt, *J* = 9.7, 4.7 Hz, CH), 3.48 (1H, dd, *J* = 15.1, 4.6 Hz, CH₂), 3.39-3.30 (1H, m, CH₂); ¹³C NMR (101 MHz, (CD₃)₂SO) δ 169.4 (C), 151.7 (C), 149.5 (C), 146.8 (C), 146.3 (C), 144.6 (C), 127.2 (2 x CH), 123.4 (2 x CH), 120.5 (CH), 119.6 (CH), 107.3 (CH), 69.6 (CH), 38.2 (CH₂); HRMS (ESI +ve) Exact mass calculated for C₁₅H₁₂N₃O₆ [M+H]⁺: 330.0721, found: 330.0714; Exact mass calculated for C₁₅H₁₁N₃NaO₆ [M+Na]⁺: 352.0540, found: 352.0528.



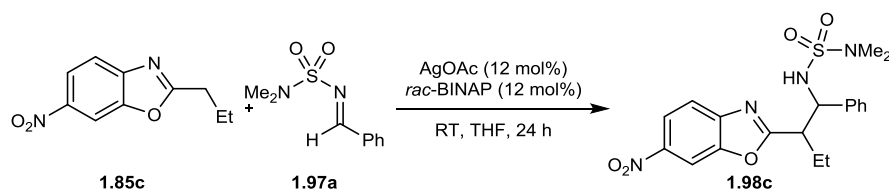
2-(6-nitro-1,3-benzoxazole-2-yl)-1-(4-nitrophenyl)propan-1-ol (**1.93.b**).

A solution of *rac*-BINAP (30.0 mg, 0.05 mmol) and AgOAc (8.00 mg, 0.05 mmol) in THF (2 mL) was stirred at room temperature for 15 min. 1,3-Benzoxazole **1.85b** (77.0 mg, 0.40 mmol) and *p*-nitrobenzaldehyde **1.92a** (46.0 mg, 0.40 mmol) were added and the reaction mixture was stirred at room temperature for 48 h. The mixture was filtered through a short plug of SiO₂, eluted with EtOAc and concentrated *in vacuo*. The crude product was obtained as a diastereomeric mixture in a 1:1 A:B ratio. Purification of the residue by column chromatography (10→80% EtOAc/petroleum ether) gave the



addition product **1.93b** as a white crystalline solid (42 mg, 31%). R_f 0.48 (40% EtOAc/petroleum ether); m.p. 187-188 °C; IR (film) 1566, 1513 (NO₂), 1345 (NO₂), 1233, 1309, 827, 735, 640 cm⁻¹; The purified product was obtained as a diastereomeric mixture in a 1:1.4 A:B ratio. ¹H NMR (400 MHz, (CD₃)₂SO) δ 8.66-8.63 (2H, m, ArH^{A+B}), 8.30-8.25 (2H, m, ArH^{A+B}), 8.22-8.16 (4H, m, ArH^{A+B}), 7.95-7.90 (2H, m, ArH^{A+B}), 7.68-7.61 (4H, m, ArH^{A+B}), 6.09 (1H, d, J = 4.6 Hz, OH^A), 6.04 (1H, d, J = 4.6 Hz, OH^B), 5.35 (1H, t, J = 4.8 Hz, CH^B), 5.09 (1H, dd, J = 7.4, 4.6 Hz, CH^A) 3.69-3.61 (1H, m, CH^B), 3.56 (1H, m, J = 7.1 Hz, CH^A), 1.29 (3H, d, J = 7.0 Hz, CH₃^B), 1.23 (3H, d, J = 7.1 Hz, CH₃^A); ¹³C NMR (126 MHz, (CD₃)₂SO) δ 173.2 (C^A), 173.0 (C^B), 150.7 (C^B), 150.5 (C^A), 149.5 (C^B), 149.4 (C^A), 146.9 (C^A), 146.7 (C^B), 146.2 (C^A), 146.2 (C^B), 144.6 (C^B), 144.5 (C^A), 128.0 (2 x CH^A), 127.4 (2 x CH^B), 123.3 (2 x CH^A), 123.2 (2 x CH^B), 120.4 (CH^A), 120.4 (CH^B), 119.7 (CH^B), 119.7 (CH^A), 107.3 (CH^A), 107.4 (CH^B), 74.7 (CH^A), 72.9 (CH^B), 42.1 (CH^A), 41.5 (CH^B), 14.6 (CH₃^A), 11.4 (CH₃^B); Exact mass calculated for C₁₆H₁₄N₃O₆ [M+H]⁺: 344.0877, found: 366.0858. Exact mass calculated for C₁₆H₁₃N₃NaO₆ [M+Na]⁺: 366.0697, found: 366.0682.

Dimethyl([2-(6-nitro-1,3-benzoxazol-2-yl)-1-phenylbutyl]sulfamoyl)amine (1.98c)



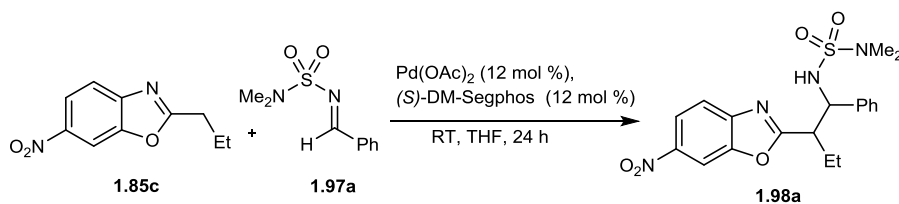
A mixture of *rac*-BINAP (30.0 mg, 0.05 mmol) and AgOAc (8.00 mg, 0.05 mmol) in THF (2 mL) was stirred at room temperature for 15 min. 1,3-benzoxazole **1.85c** (82.0 mg, 0.40 mmol) and *N*-sulfamoyl imine **1.97a** (85.0 mg, 0.04 mmol) were added and the reaction was stirred at room temperature for 24 h. The mixture was filtered through a short plug of SiO₂, eluted with EtOAc and concentrated *in vacuo*. Purification of the residue by column chromatography (1 → 2% MeOH/DCM) gave the addition product **1.98c** (85.7mg, 51%) as a yellow oil. R_f 0.16 (1% MeOH/DCM). The desired product was obtained as a diastereomeric mixture in a 73:27 ratio A:B. ¹H NMR (500 MHz, CDCl₃) δ 8.38 (1H, d, J = 2.1 Hz, ArH^B), 8.34



(1H, d, $J = 2.1$ Hz, ArH^A), 8.31 (1H, dd, $J = 8.8, 2.1$ Hz, ArH^B), 8.26 (1H, dd, $J = 8.8, 2.1$ Hz, ArH^A), 7.82 (1H, d, $J = 8.8$ Hz, ArH^B), 7.73 (1H, d, $J = 8.7$ Hz, ArH^A), 7.31-7.10 (10H, m, ArH^{A+B}), 6.13 (1H, 1d, $J = 9.1$ Hz, NHSO₂^B), 5.77 (1H, d, $J = 9.0$ Hz, NHSO₂^A), 4.85-4.76 (2H, m, PhCH^{A+B}NH), 3.48 (1H, ddd, $J = 10.0, 7.4, 4.7$ Hz, CH^ACH₂CH₃), 3.35 (1H, ddd, $J = 9.7, 6.3, 5.6$ Hz, CH^BCH₂CH₃), 2.51 (6H, s, N(CH₃)₂^A), 2.47 (6H, s, N(CH₃)₂^B), 2.17-1.82 (3H, m, CH₂^A, CH₂^B), 1.93-1.83 (1H, m, CH₂^B), 0.99-0.92 (6H, m, CH₂CH₃^{A+B}); ¹³C NMR (125.8 MHz, CDCl₃) δ 171.6 (C^B), 170.8 (C^A), 149.4 (C^A), 149.4 (C^B), 145.9 (C^A), 145.8 (C^B), 145.2 (C^B), 145.0 (C^A), 140.3 (C^B), 139.0 (C^A), 128.8 (2 x CH^B), 128.6 (2 x CH^A), 128.2 (CH^A), 128.1 (CH^B), 126.7 (2 x CH^A), 126.4 (2 x CH^B), 120.6 (CH^B), 120.5 (CH^A), 119.8 (CH^{A+B}), 107.3 (CH^B), 107.1 (CH^A), 60.2 (CH^A), 59.7 (CH^B), 49.2 (CH^B), 49.2 (CH^A), 38.3 (2 x CH₃^B), 37.6 (2 x CH₃^A), 25.2 (CH₂^B), 22.9 (CH₂^B), 11.9 (2 x CH₃).

Preparation of a chiral product:

Dimethyl([2-(6-nitro-1,3-benzoxazol-2-yl)-1-phenylbutyl]sulfamoyl)amine (1.98a)



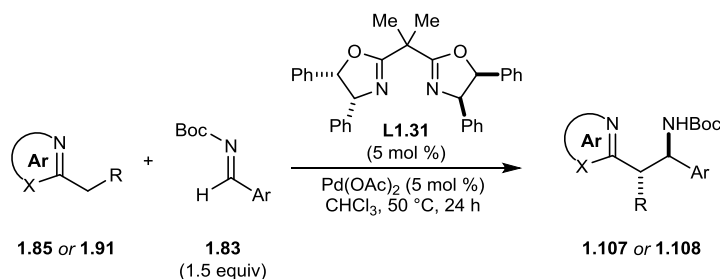
A mixture of (S)-DM-SEGPHOS (43.0 mg, 0.06 mmol) and Pd(OAc)₂ (13.0 mg, 0.06 mmol) in THF (2.5 mL) was stirred at room temperature for 15 min. 1,3-benzoxazole **1.85c** (103 mg, 0.50 mmol) and *N*-sulfamoyl imine **1.97a** (106 mg, 0.50 mmol) were added and the reaction was stirred at room temperature for 24 h. The mixture was filtered through a short plug of SiO₂, eluted with EtOAc and concentrated *in vacuo*. Purification of the residue by column chromatography (1 → 2% MeOH/DCM) gave the addition product **1.98c** (108 mg, 52%) as a yellow oil. *R*_f 0.16 (1% MeOH/DCM). The desired product was obtained as a diastereomeric mixture in a >19:1 ratio. ¹H NMR (500 MHz, CDCl₃) δ 8.37 (1H, d, $J = 2.0$ Hz, ArH); 8.32 (1H, dd, $J = 8.8, 2.1$ Hz, ArH), 7.83 (1H, d, $J = 8.8$ Hz, ArH), 7.33-7.24 (3H, m, ArH), 7.23-7.17 (2H, m, ArH), 6.01 (1H, d, $J = 8.9$ Hz, NHSO₂), 4.84 (1H,



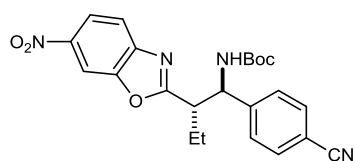
dd, $J = 8.9, 6.1$ Hz, PhCHNH), 3.33 (1H, dt, $J = 9.4, 5.8$ Hz, CCHCHPh), 2.50 (6H, s, N(CH₃)₂), 2.12-2.00 (1H, m, CH₂), 2.00-1.86 (1H, m, CH₂), 0.97 (3, t, $J = 7.44$ Hz, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 171.5 (C), 149.4 (C), 145.8 (C), 145.2 (C), 140.4 (C), 128.9 (2 x CH), 128.2 (CH), 126.3 (2 x CH), 120.7 (CH), 119.8 (CH), 107.3 (CH), 59.6 (CH), 49.3 (CH), 37.6 (CH₂), 25.4 (CH₂), 11.9 (2 x CH₃).

Pd(II)-Catalysed addition reactions to imines

General Procedure A



To a mixture of the appropriate alkylazaarene (0.50 mmol) and the appropriate *N*-Boc imine (0.75 mmol) at room temperature was added a solution of Pd(OAc)₂ (5.5 mg, 25 μ mol) and ligand **L1.31** (12.2 mg, 25.1 μ mol) in CHCl₃ (0.5 mL, alcohol-free, amylene-stabilized). The reaction mixture was stirred at room temperature for 24 h, filtered through a short plug of silica gel using 30% acetone/hexane as eluent, and concentrated *in vacuo*. Purification of the residue by column chromatography gave the addition product as a single diastereoisomer.

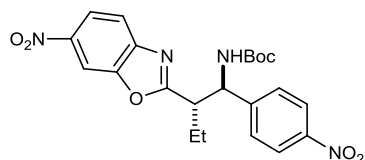


tert-Butyl *N*-[(1*R*,2*S*)-1-(4-cyanophenyl)-2-(6-nitro-1,3-benzoxazol-2-yl)butyl]carbamate (**1.107b**).

The title compound was prepared according to General Procedure A from alkylazaarene **1.85c** (103 mg, 0.50 mmol) and *N*-Boc imine **1.83b** (173 mg, 0.75 mmol) and purified by column chromatography (2→12% acetone/hexane) to give a white solid (189 mg, 87%). R_f 0.17 (20% acetone/hexane); m.p. 86-88 °C; $[\alpha]_D^{20} +32$ (c 1.01, CHCl₃); IR (film) 2230 (C≡N), 1713 (C=O), 1562, 1526 (NO₂), 1502, 1366, 1344 (NO₂), 1267, 1250, 1157 cm⁻¹; ¹H NMR (500 MHz, CD₃OD) δ 8.54 (1H, d, $J = 1.9$ Hz, ArH), 8.33 (1H, dd, $J = 8.8, 1.9$ Hz, ArH), 7.87 (1H, d, $J = 8.8$ Hz, ArH), 7.72 (2H, d, $J = 8.1$ Hz, ArH), 7.57 (2H, d, $J = 8.2$ Hz,



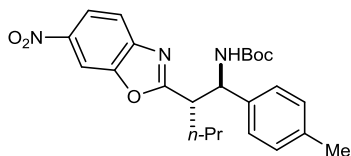
ArH), 5.17 (1H, d, $J = 8.8$ Hz, CHN), 3.53 (1H, ddd, $J = 9.8, 9.7, 4.6$ Hz, CHCH₂CH₃), 1.95-1.80 (1H, m, CH₂CH₃), 1.66-1.53 (1H, m, CH₂CH₃), 1.24 (9H, s, C(CH₃)₃), 0.84 (3H, t, $J = 7.4$ Hz, CH₂CH₃); ¹³C NMR (125.8 MHz, CD₃OD) δ 173.3 (C), 157.1 (C), 151.2 (C), 147.4 (C), 147.3 (C), 146.7 (C), 133.7 (2 x CH), 129.3 (2 x CH), 121.6 (CH), 120.8 (CH), 119.4 (C), 112.7 (C), 108.3 (CH), 80.7 (C), 58.3 (CH), 49.1 (CH), 28.5 (3 x CH₃), 25.5 (CH₂), 11.9 (CH₃); HRMS (ESI +ve) Exact mass calculated for C₂₃H₂₅N₄O₅ [M+H]⁺: 437.1820, found: 437.1826. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (90:10 hexane:EtOH, 2.0 mL/min, 230 nm, 25 °C); t_r (major) = 9.2 min, t_r (minor) = 12.9 min; 87% ee.



tert-Butyl N-[(1R,2S)-2-(6-nitro-1,3-benzoxazol-2-yl)-1-(4-nitrophenyl)butyl]carbamate (1.107c).

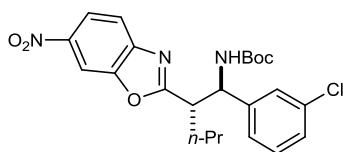
The title compound was prepared according to General Procedure A from alkylazaarene **1.85c** (103 mg, 0.50 mmol) and *N*-Boc imine **1.83c** (188 mg, 0.75 mmol) and purified by column chromatography (2→12% acetone/hexane) to give a white solid (213 mg, 93%). R_f 0.17 (20% acetone/hexane); m.p. 82-84 °C; [α]_D²⁰ +27 (c 1.01, CHCl₃); IR (film) 1711 (C=O), 1564, 1522 (NO₂), 1344 (NO₂), 1267, 1250, 1157, 856, 852, 735 cm⁻¹; ¹H NMR (500 MHz, CD₃OD) δ 8.53 (1H, d, $J = 2.0$ Hz, ArH), 8.33 (1H, dd, $J = 8.8, 2.0$ Hz, ArH), 8.22 (2H, d, $J = 8.5$ Hz, ArH), 7.87 (1H, d, $J = 8.8$ Hz, ArH), 7.63 (2H, d, $J = 8.7$ Hz, ArH), 5.23 (1H, d, $J = 8.7$ Hz, CHN), 3.56 (1H, ddd, $J = 9.8, 9.7, 4.6$ Hz, CHCH₂CH₃), 1.96-1.83 (1H, m, CH₂CH₃), 1.67-1.56 (1H, m, CH₂CH₃), 1.25 (9H, s, C(CH₃)₃), 0.85 (3H, t, $J = 7.4$ Hz, CH₂CH₃); ¹³C NMR (125.8 MHz, CD₃OD) δ 173.2 (C), 157.1 (C), 151.2 (C), 149.2 (C), 148.9 (C), 147.3 (C), 146.7 (C), 129.4 (2 x CH), 124.8 (2 x CH), 121.6 (CH), 120.8 (CH), 108.3 (CH), 80.8 (C), 58.0 (CH), 49.2 (CH) 28.5 (3 x CH₃), 25.5 (CH₂), 11.9 (CH₃); HRMS (ESI +ve) Exact mass calculated for C₂₂H₂₅N₄O₇ [M+H]⁺: 457.1718, found: 457.1718. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (80:20 hexane:*i*-PrOH, 2.0 mL/min, 230 nm, 25 °C); t_r (major) = 7.2 min, t_r (minor) = 22.6 min; 97% ee.





***tert*-Butyl *N*-[(1*R*,2*S*)-1-(4-methylphenyl)-2-(6-nitro-1,3-benzoxazol-2-yl)pentyl]carbamate (1.107d).**

The title compound was prepared according to General Procedure A from alkylazaarene **1.85d** (110 mg, 0.50 mmol) and *N*-Boc imine **1.83d** (164 mg, 0.75 mmol) and purified by column chromatography (2→12% acetone/hexane) to give a white solid (190 mg, 86%). R_f 0.34 (20% acetone/hexane); m.p. 58-60 °C; $[\alpha]_D^{20} +31$ (c 1.05, CHCl_3); IR (film) 1718 (C=O), 1602, 1577, 1520 (NO_2), 1454, 1350 (NO_2), 1267, 1162, 765 cm^{-1} ; ^1H NMR (500 MHz, CD_3OD) δ 8.53 (1H, d, $J = 1.9$ Hz, ArH), 8.32 (1H, dd, $J = 8.7, 1.8$ Hz, ArH), 7.85 (1H, d, $J = 8.8$ Hz, ArH), 7.23 (2H, d, $J = 8.0$ Hz, ArH), 7.16 (2H, d, $J = 7.9$ Hz, ArH), 4.99 (1H, d, $J = 9.3$ Hz, CHN), 3.53 (1H, ddd, $J = 10.7, 9.7, 4.2$ Hz, $\text{CHCH}_2\text{CH}_2\text{CH}_3$), 2.32 (3H, s, ArCH₃), 1.91-1.76 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.50-1.42 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.27-1.13 (2H, m, CH_2CH_3), 1.19 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.80 (3H, t, $J = 7.3$ Hz, CH_2CH_3); ^{13}C NMR (125.8 MHz, CD_3OD) δ 174.3 (C), 157.1 (C), 151.2 (C), 147.4 (C), 146.6 (C), 138.8 (C), 138.7 (C), 130.4 (2 x CH), 128.1 (2 x CH), 121.5 (CH), 120.6 (CH), 108.3 (CH), 80.3 (C), 58.7 (CH), 48.0 (CH), 58.7 (CH), 34.3 (CH_2), 28.5 (3 x CH_3), 21.5 (CH_2), 21.1 (CH_3), 13.9 (CH_3); HRMS (ESI +ve) Exact mass calculated for $\text{C}_{24}\text{H}_{30}\text{N}_3\text{O}_5$ $[\text{M}+\text{H}]^+$: 440.2180, found: 440.2180. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (80:20 hexane:*i*-PrOH, 2.0 mL/min, 230 nm, 25 °C); t_r (minor) = 6.8 min, t_r (major) = 7.9 min; 84% ee.



***N*-*tert*-Butyl *N*-[(1*R*,2*S*)-2-(1,3-benzoxazol-2-yl)-1-(3-chlorophenyl)pentyl]carbamate (1.107e).**

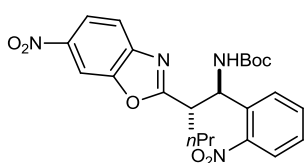
The title compound was prepared according to a slight modification of General Procedure A (in that the reaction temperature was 60 °C) from alkylazaarene **1.85d** (110 mg, 0.50 mmol) and *N*-Boc imine **1.85e** (180 mg, 0.75 mmol) and purified by column chromatography (2→12% acetone/hexane) to give a 96:4 inseparable mixture of diastereomers as a white solid (190 mg, 83%). R_f 0.26 (20% acetone/hexane); m.p. 58-60 °C; $[\alpha]_D^{20} +23$ (c 1.05, CHCl_3); IR (film) 2930, 2870, 1713 (C=O), 1562, 1525 (NO_2), 1365, 1342 (NO_2), 1267, 1234, 1161 cm^{-1} .



Major diastereomer: ^1H NMR (500 MHz, CD_3OD) δ 8.49 (1H, d, $J = 2.1$ Hz, ArH), 8.29 (1H, dd, $J = 8.8, 2.1$ Hz, ArH), 7.84 (1H, d, $J = 8.8$ Hz, ArH), 7.46-7.37 (1H, m, ArH), 7.35-7.25 (3H, m, ArH), 5.07 (1H, d, $J = 9.1$ Hz, CHN), 3.57 (1H, ddd, $J = 10.5, 9.3, 4.3$ Hz, CHCH₂CH₂CH₃), 1.92-1.79 (1H, m, CH₂CH₂CH₃), 1.52-1.42 (1H, m, CH₂CH₂CH₃), 1.30-1.15 (CH₂CH₃), 1.21 (9H, s, C(CH₃)₃), 0.80 (3H, t, $J = 7.3$ Hz, CH₂CH₃); ^{13}C NMR (125.8 MHz, CD_3OD) δ 173.8 (C), 157.1 (C), 151.1 (C), 147.3 (C), 146.7 (C), 144.2 (C), 135.7 (C), 131.3 (CH), 129.0 (CH), 128.3 (CH), 126.7 (CH), 121.6 (CH), 120.7 (CH), 108.3 (CH), 80.6 (C), 58.4 (CH), 47.6 (CH), 34.3 (CH₂), 28.5 (3 x CH₃), 21.5 (CH₂), 13.9 (CH₃).

Minor diastereomer (diagnostic peaks): ^1H NMR (500 MHz, CD_3OD) δ 8.43 (1H, d, $J = 2.1$ Hz, ArH), 8.23 (2H, dd, $J = 8.8, 2.1$ Hz, ArH), 7.72 (1H, d, $J = 8.8$ Hz, ArH), 7.18-7.08 (3H, m, ArH), 2.08-1.98 (1H, m, CH₂CH₂CH₃).

HRMS (ESI +ve) Exact mass calculated for $\text{C}_{23}\text{H}_{27}\text{ClN}_3\text{O}_5$ $[\text{M}+\text{H}]^+$: 460.1634, found: 460.1633. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (80:20 hexane:*i*-PrOH, 2.0 mL/min, 230 nm, 25 °C); t_r (major) = 3.6 min, t_r (minor) = 6.8 min; 89% ee.

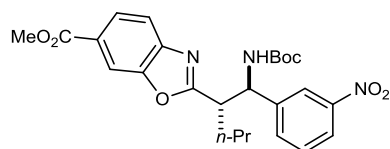


tert-Butyl N-[(1R,2S)-2-(1,3-benzoxazol-2-yl)-1-(2-nitrophenyl)pentyl]carbamate (1.107f).

The title compound was prepared according to a modification of General Procedure A (in that the reaction temperature was 50 °C) from alkylazaarene **1.85d** (110 mg, 0.50 mmol) and *N*-Boc imine **1.83f** (188 mg, 0.75 mmol) and purified by column chromatography (2→12% acetone/hexane) to give a white solid (165 mg, 70%). R_f 0.23 (20% acetone/hexane); m.p. 86-88 °C; $[\alpha]_D^{20} -27$ (c 0.98, CHCl_3); IR (film) 2974, 1701 (C=O), 1564, 1530 (NO_2), 1364, 1346 (NO_2), 1269, 1250, 1165, 824, 760 cm^{-1} ; ^1H NMR (500 MHz, CD_3OD) δ 8.44 (1H, br s, ArH), 8.26 (1H, dd, $J = 8.8, 2.2$ Hz, ArH), 7.75-7.60 (4H, m, ArH), 7.39 (1H, t, $J = 8.0$ Hz, ArH), 5.82 (1H, d, $J = 8.6$ Hz, CHN), 3.69-3.60 (1H, m, CHCH₂CH₂CH₃), 2.17-2.04 (1H, m, CH₂CH₂CH₃), 1.98-1.90 (1H, m, CH₂CH₂CH₃), 1.42-1.19 (2H, m, CH₂CH₃), 1.38 (9H, s, C(CH₃)₃), 0.90 (3H, t, $J = 7.3$ Hz, CH₂CH₃); ^{13}C NMR (125.8 MHz, CD_3OD) δ 172.7 (C), 157.4 (C), 151.1 (C), 150.2 (C), 147.0 (C), 146.7 (C), 136.3 (C), 134.2 (CH), 130.6 (CH), 129.9 (CH),

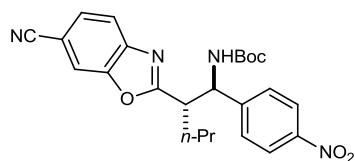


125.4 (CH), 121.5 (CH), 120.7 (CH), 108.2 (CH), 80.8 (C), 53.7 (CH), 47.3 (CH), 32.4 (CH₂), 28.6 (3 x CH₃), 21.6 (CH₂), 14.1 (CH₃); HRMS (ESI +ve) Exact mass calculated for C₂₃H₂₇N₄O₇ [M+H]⁺: 471.1874, found: 471.1875. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (90:10 hexane:*i*-PrOH, 2.0 mL/min, 230 nm, 25 °C); t_r (major) = 13.2 min, t_r (minor) = 19.7 min; 94% ee.



Methyl 2-[(1R,2S)-1-[(*tert*-butoxy)carbonyl]amino]-1-(3-nitrophenyl)pentan-2-yl]-1,3-benzoxazole-6-carboxylate (1.107g)

The title compound was prepared according to a modification of General Procedure A (in that the reaction temperature was 50 °C) from alkylazaarene **1.85g** (117 mg, 0.50 mmol) and *N*-Boc imine **1.83g** (188 mg, 0.75 mmol) and purified by column chromatography (2→12% acetone/hexane) to give a white solid (194 mg, 87%). R_f 0.22 (20% acetone/hexane); m.p. 62-64 °C; [α]_D²⁰ +24 (*c* 1.0, CHCl₃); IR (film) 2960, 1719 (C=O), 1533 (NO₂), 1502, 1438, 1352 (NO₂), 1292, 1166, 1078, 760 cm⁻¹; ¹H NMR (500 MHz, CD₃OD) δ 8.29 (1H, t, *J* = 1.9 Hz, ArH), 8.22 (1H, d, *J* = 0.7 Hz, ArH), 8.19-8.15 (1H, br d, ArH), 8.08 (1H, dd, *J* = 8.3, 0.9 Hz, ArH), 7.77 (2H, t, *J* = 8.8 Hz, ArH), 7.61 (1H, t, *J* = 7.9 Hz, ArH), 5.21 (1H, d, *J* = 8.9 Hz, CHN), 3.95 (3H, s, OCH₃), 3.62 (1H, ddd, *J* = 10.7, 9.0, 4.4 Hz, CHCH₂CH₂CH₃), 1.95-1.83 (1H, m, CH₂CH₂CH₃), 1.55-1.42 (1H, m, CH₂CH₂CH₃), 1.29-1.16 (2H, m, CH₂CH₃), 1.23 (9H, s, C(CH₃)₃), 0.82 (3H, t, *J* = 7.3 Hz, CH₂CH₃); ¹³C NMR (125.8 MHz, CD₃OD) δ 171.5 (C), 167.9 (C), 157.2 (C), 151.6 (C), 149.9 (C), 145.9 (C), 144.4 (C), 134.6 (CH), 131.0 (CH), 128.5 (C), 127.3 (CH), 123.7 (CH), 123.0 (CH), 120.3 (CH), 113.2 (CH), 80.7 (C), 58.2 (CH), 52.9 (CH₃), 47.3 (CH), 34.4 (CH₂), 28.4 (3 x CH₃), 21.5 (CH₂), 13.9 (CH₃); HRMS (ESI +ve) Exact mass calculated for C₂₅H₃₀N₃O₇ [M+H]⁺: 484.2078, found: 484.2073. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (60:40 hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 6.5 min, t_r (minor) = 8.5 min; 88% ee.



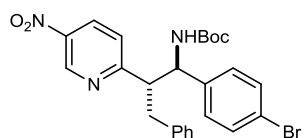
***tert*-Butyl N-[(1R,2S)-2-(6-cyano-1,3-benzoxazol-2-yl)-1-(4-nitrophenyl)pentyl]carbamate (1.107h).**

The title compound was prepared according to a



modification of General Procedure A (in that the reaction temperature was 50 °C) from alkylazaarene **1.85h** (100 mg, 0.50 mmol) and *N*-Boc imine **1.83c** (188 mg, 0.75 mmol) and purified by column chromatography (2→12% acetone/hexane) to give a white solid (222 mg, 99%). *R*_f 0.20 (20% acetone/hexane); m.p. 60-62 °C; [α]_D²⁰ +29 (*c* 1.02, CHCl₃); IR (film) 2968, 2232 (CN), 1711 (C=O), 1604, 1524 (NO₂), 1431, 1348 (NO₂), 1107, 1246, 1163, 830, 758 cm⁻¹; ¹H NMR (500 MHz, CD₃OD) δ 8.23 (2H, d, *J* = 8.6 Hz, ArH), 8.07 (1H, s, ArH), 7.85 (1H, d, *J* = 8.2 Hz, ArH), 7.73 (1H, d, *J* = 8.3 Hz, ArH), 7.64-7.60 (2H, m, ArH), 5.20 (1H, d, *J* = 8.8 Hz, CHN), 3.56 (1H, td, *J* = 10.2, 4.4 Hz, CHCH₂CH₂CH₃), 1.94-1.81 (1H, m, CH₂CH₂CH₃), 1.53-1.44 (1H, m, CH₂CH₂CH₃), 1.32-1.13 (2H, m, CH₂CH₃), 1.24 (9H, s, C(CH₃)₃), 0.82 (3H, t, *J* = 7.3 Hz, CH₂CH₃); ¹³C NMR (125.8 MHz, CD₃OD) δ 171.9 (C), 157.1 (C), 151.3 (C), 149.3 (C), 148.9 (C), 145.9 (C), 130.0 (CH), 129.4 (2 x CH), 124.9 (2 x CH), 121.8 (CH), 119.5 (C), 116.4 (CH), 109.5 (C), 80.8 (C), 58.3 (CH), 47.2 (CH), 34.3 (CH₂), 28.4 (3 x CH₃), 21.5 (CH₂), 13.9 (CH₃); HRMS (ESI +ve) Exact mass calculated for C₂₄H₂₇N₄O₅ [M+H]⁺: 451.1976, found: 451.1975. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (85:15 hexane:EtOH, 2.0 mL/min, 254 nm, 25 °C); *t*_r (major) = 6.4 min, *t*_r (minor) = 8.9 min, 91% ee.

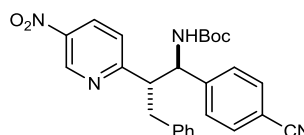




***tert*-Butyl**

***N*-[(1*R*,2*S*)-1-(4-bromophenyl)-2-(5-nitropyridin-2-yl)-3-phenylpropyl]carbamate (1.108a).**

The title compound was prepared according to a slight modification of General Procedure A (in that the reaction temperature was 50 °C) from alkylazaarene **1.91b** (114 mg, 0.50 mmol) and *N*-Boc imine **1.83b** (213 mg, 0.75 mmol) and purified by column chromatography (2→12% acetone/hexane) to give a white crystalline solid (215 mg, 84%). *R*_f 0.37 (20% acetone/hexane), m.p. 70-72 °C; $[\alpha]_{\text{D}}^{20} +14$ (*c* 1.02, CHCl₃); IR (film) 1709 (C=O), 1599, 1578, 1524 (NO₂), 1487, 1348 (NO₂), 1244, 1165, 1009, 858 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.46 (1H, s, ArH), 8.08 (1H, d, *J* = 7.0 Hz, ArH), 7.31-7.27 (2H, m, ArH), 7.24-7.13 (3H, m, ArH), 6.99 (2H, d, *J* = 6.0 Hz, ArH), 6.89 (2H, d, *J* = 7.7 Hz, ArH), 6.58 (1H, d, *J* = 8.2 Hz, ArH), 5.12 (1H, br s, CHN), 3.48 (1H, br s, CHCH₂Ph), 3.24-3.17 (2H, m, CH₂Ph), 1.47 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 167.4 (C), 155.4 (C), 144.4 (CH), 142.9 (C), 140.8 (C), 138.5 (C), 131.4 (CH), 131.0 (CH), 128.8 (2 x CH), 128.6 (2 x CH), 127.6 (2 x CH), 126.6 (2 x CH), 125.2 (CH), 120.9 (C), 79.8 (C), 57.0 (CH), 55.0 (CH), 39.5 (CH₂), 28.4 (3 x CH₃); HRMS (ESI +ve) Exact mass calculated for C₂₅H₂₆BrN₃NaO₄ [M+Na]⁺: 534.0999, found: 534.0992. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (90:10 hexane:EtOH, 2.0 mL/min, 230 nm, 25 °C); major diastereoisomer: *t*_r (major) = 4.3 min, *t*_r (minor) = 7.3 min; 98% ee.



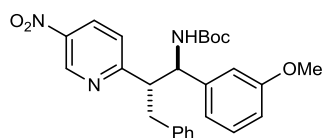
***tert*-Butyl**

***N*-[(1*R*,2*S*)-1-(4-cyanophenyl)-2-(5-nitropyridin-2-yl)-3-phenylpropyl]carbamate (1.108b).**

The title compound was prepared according to a slight modification of General Procedure A (in that the reaction temperature was 50 °C) from alkylazaarene **1.91b** (114 mg, 0.50 mmol) and *N*-Boc imine **1.83b** (173 mg, 0.75 mmol) and purified by column chromatography (2→12% acetone/hexane) to give a white crystalline solid (190 mg, 80%). *R*_f 0.13 (20% acetone/hexane); m.p. 208-210 °C; $[\alpha]_{\text{D}}^{20} +1.0$ (*c* 1.03, (CH₃)₂CO); IR (film) 3367 (NH), 2229 (C≡N), 1711 (C=O), 1601, 1578, 1516 (NO₂), 1348 (NO₂), 1250, 1163, 858 cm⁻¹; ¹H NMR (500 MHz, (CD₃)₂SO) δ 9.36 (1H, br s, ArH), 8.40 (1H, dd, *J* = 8.5, 2.6 Hz, ArH), 7.84 (2H, d, *J* = 7.8 Hz, ArH), 7.63 (2H, d, *J* = 8.1 Hz, ArH), 7.46 (1H, d, *J* = 9.2 Hz,



ArH), 7.26 (1H, d, $J = 8.5$ Hz, ArH), 7.08 (2H, t, $J = 7.2$ Hz, ArH), 6.80 (2H, d, $J = 7.1$ Hz, ArH), 5.02 (1H, t, $J = 9.2$ Hz, CHN), 3.73-3.62 (1H, m, CHCH₂Ph), 3.03 (1H, t, $J = 12.3$ Hz, CH₂Ph), 2.54 (1H, dd, $J = 13.5, 2.9$ Hz, CH₂Ph), 1.19 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂SO) δ 167.3 (C), 154.4 (C), 147.6 (C), 144.1 (CH), 142.8 (C), 138.7 (C), 132.4 (2 x CH), 131.0 (CH), 128.4 (2 x CH), 128.3 (2 x CH), 128.1 (2 x CH), 126.0 (CH), 125.6 (CH), 118.8 (C), 110.1 (C), 78.2 (C), 58.1 (CH), 53.6 (CH), 37.6 (CH₂), 27.9 (3 x CH₃); HRMS (ESI +ve) Exact mass calculated for C₂₆H₂₇N₄O₄ [M+H]⁺: 459.2027, found: 459.2027. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (80:20 hexane:*i*-PrOH, 1.0 mL/min, 230 nm, 25 °C); t_r (major) = 6.2 min, t_r (minor) *ca.* 17.5 min (not observed), >99% ee.



***tert*-Butyl *N*-[(1*R*,2*S*)-1-(3-methoxyphenyl)-2-(5-nitropyridin-2-yl)-3-phenylpropyl]carbamate (1.108j).**

The title compound was prepared according to a slight modification of General Procedure A (in that the reaction temperature was 50 °C) from alkylazaarene **1.91b** (114 mg, 0.50 mmol) and *N*-Boc imine **1.83i** (176 mg, 0.75 mmol) and purified by column chromatography (2→12% acetone/hexane) to give a 93:7 inseparable mixture of diastereomers as a white solid (219 mg, 94%). R_f 0.16 (20% acetone/hexane); m.p. 128-130 °C; $[\alpha]_D^{20} +1.6$ (c 4.87, CH₂Cl₂); IR (film) 2978, 1708 (C=O), 1560, 1524 (NO₂), 1494, 1350 (NO₂), 1251, 1167, 858, 761 cm⁻¹.

Major diastereomer: ¹H NMR (500 MHz, CD₃OD) δ 9.38 (1H, br s, ArH), 8.23 (1H, dd, $J = 8.5, 2.7$ Hz, ArH), 7.23 (1H, t, $J = 7.8$ Hz, ArH), 7.16-7.00 (4H, m, ArH), 6.97-6.80 (5H, m, ArH), 5.02 (1H, d, $J = 8.1$ Hz, CHN), 3.77 (3H, s, OCH₃), 3.66-3.31 (1H, m, CHCH₂Ph), 3.06 (1H, dd, $J = 13.3, 10.6$ Hz, CH₂Ph) 2.86 (1H, dd, $J = 13.5, 4.5$ Hz, CH₂Ph), 1.31 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, CD₃OD) δ 169.4 (C), 161.4 (C), 157.2 (C), 145.4 (CH), 144.6 (C), 144.4 (C), 140.4 (C), 132.0 (CH), 130.6 (CH), 129.9 (2 x CH), 129.3 (2 x CH), 127.2 (CH), 126.8 (CH) 120.3 (CH), 113.8 (CH), 113.7 (CH), 80.3 (C), 59.5 (CH), 56.4 (CH), 55.7 (CH₃), 39.9 (CH₂), 28.6 (3 x CH₃).



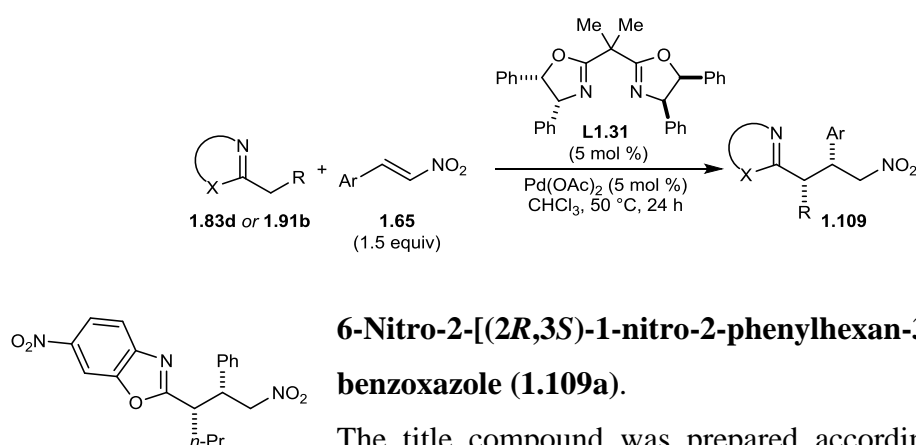
Minor diastereomer (diagnostic peaks): ^1H NMR (500 MHz, CD_3OD) δ 9.24 (1H, d, $J = 2.3$ Hz, ArH), 8.04 (1H, dd, $J = 8.5, 2.5$ Hz, ArH), 6.79-6.69 (2H, m, ArH), 6.62 (1H, ddd, $J = 8.2, 2.5, 0.5$ Hz, ArH), 5.09 (1H, d, $J = 10.0$ Hz, CHN), 3.39 (1H, dd, $J = 13.4, 2.9$ Hz, CH_2Ph), 3.18 (1H, dd, $J = 13.4, 11.5$ Hz, CH_2Ph), 1.46 (9H, $\text{C}(\text{CH}_3)_3$). HRMS (ESI +ve) Exact mass calculated for $\text{C}_{26}\text{H}_{30}\text{N}_3\text{O}_5$ $[\text{M}+\text{H}]^+$: 464.2180, found: 464.2179. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (90:10 hexane:*i*-PrOH, 2.0 mL/min, 230 nm, 25 °C); t_r (major) = 7.2 min, t_r (minor) = 21.7 min; 93% ee.



Pd(II)-Catalysed Addition Reactions to Nitroalkenes

General Procedure B

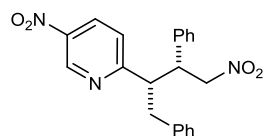
To a mixture of the appropriate alkylazaarene (0.50 mmol) and the appropriate nitroalkene (0.75 mmol) at room temperature was added a solution of Pd(OAc)₂ (5.5 mg, 25 μmol) and ligand **L1.31** (12.2 mg, 25.1 μmol) in CHCl₃ (0.5 mL, alcohol-free, amylene-stabilised). The reaction mixture was stirred at 50 °C for 24 h, filtered through a short plug of silica gel using 30% acetone/hexane as eluent, and concentrated *in vacuo*. Purification of the residue by column chromatography gave the addition product.



The title compound was prepared according to General Procedure B from alkylazaarene **1.83d** (110 mg, 0.50 mmol) and nitroalkene **1.65a** (112 mg, 0.75 mmol) and purified by column chromatography (2→12% acetone/hexane) to give a yellow oil (107 mg, 58%). *R*_f 0.33 (20% acetone/hexane); [*α*]_D²⁰ +8.0 (*c* 0.98, CHCl₃); IR (film) 3107, 2963, 1557, 1527 (NO₂), 1456, 1344 (NO₂), 1267, 825, 764, 702 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.45 (1H, d, *J* = 2.0 Hz, ArH), 8.33 (1H, dd, *J* = 8.8, 2.1 Hz, ArH), 7.83 (1H, d, *J* = 8.7 Hz, ArH), 7.40-7.30 (3H, m, ArH), 7.25-7.21 (2H, m, ArH), 4.77 (1H, dd, *J* = 12.9, 10.0 Hz, CH₂N), 4.58 (1H, dd, *J* = 12.9, 4.8 Hz, CH₂N), 4.02 (1H, app td, *J* = 9.9, 4.9 Hz, CHPh), 3.48 (1H, app td, *J* = 10.3, 3.9 Hz, CHCH₂CH₂CH₃), 1.88-1.75 (1H, m, CH₂CH₂CH₃), 1.62-1.51 (1H, m, CH₂CH₂CH₃), 1.22-1.11 (2H, m, CH₂CH₃), 0.78 (3H, t, *J* = 7.3 Hz, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 171.8 (C), 149.7 (C), 146.0 (C), 145.4 (C), 137.0 (C), 129.3 (2 x CH), 128.5 (CH), 127.8 (2 x CH), 120.8 (CH), 120.1 (CH), 107.4 (CH), 78.5 (CH₂), 47.3 (CH), 43.6 (CH), 33.9 (CH₂), 20.2

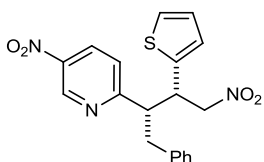


(CH₂), 13.6 (CH₃); HRMS (ESI +ve) Exact mass calculated for C₁₉H₁₉N₃O₅ [M+H]⁺: 369.1319, found: 369.1316. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (95:5 hexane:EtOH, 2.0 mL/min, 254 nm, 25 °C); t_r (major) = 13.0 min, t_r (minor) = 14.2 min, 90% ee.



5-Nitro-2-[(2R,3S)-4-nitro-1,3-diphenylbutan-2-yl]pyridine (1.109b).

The title compound was prepared according to General Procedure B from alkylazaarene **1.91b** (114 mg, 0.50 mmol) and nitroalkene **1.65a** (112 mg, 0.75 mmol) and purified by column chromatography (2→12% acetone/hexane) to give a pale yellow solid (138 mg, 73%). Slow diffusion of hexane into a solution of **1.109b** in chlorobenzene gave crystals that were suitable for X-ray diffraction. R_f 0.14 (20% acetone/hexane); m.p. 126-128 °C; [α]_D²⁰ -51 (c 1.03, CHCl₃); IR (film) 3030, 2928, 1601, 1553, 1524 (NO₂), 1495, 1379, 1352 (NO₂), 858, 760 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.49 (1H, d, *J* = 2.5 Hz, ArH), 8.20 (1H, dd, *J* = 8.5, 2.7 Hz, ArH), 7.44-7.39 (2H, m, ArH), 7.38-7.29 (3H, m, ArH), 7.13-7.05 (3H, m, ArH), 6.86 (1H, dd, *J* = 8.4, 0.3 Hz, ArH), 6.75-6.67 (2H, m, ArH), 4.58 (1H, dd, *J* = 12.6, 9.8 Hz, CH₂N), 4.04 (1H, dd, *J* = 12.6, 4.5 Hz, CH₂N), 4.17 (1H, td, *J* = 9.9, 4.4 Hz, CHCH₂N), 3.53 (1H, td, *J* = 9.8, 5.3 Hz, CHCH₂Ph), 2.94-2.84 (2H, m, CH₂Ph); ¹³C NMR (125.8 MHz, CDCl₃) δ 167.3 (C), 145.3 (CH), 142.9 (C), 138.4 (C), 137.8 (C), 131.0 (CH), 129.3 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 128.3 (CH), 128.0 (2 x CH), 126.4 (CH), 124.9 (CH), 78.6 (CH₂), 53.4 (CH), 48.2 (CH), 40.2 (CH₂); HRMS (ESI +ve) Exact mass calculated for C₂₁H₁₉N₃O₄ [M+H]⁺: 377.1370, found: 377.1372. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (70:30 hexane:EtOH, 1.0 mL/min, 210 nm, 25 °C); t_r (major) = 9.0 min, t_r (minor), *ca.* 9.5 min, >99% ee.



5-Nitro-2-[(2S,3S)-4-nitro-1-phenyl-3-(thiophen-2-yl)butan-2-yl]pyridine (1.109c).

The title compound was prepared according to a slight modification of General Procedure B (in that the reaction temperature was 60 °C and the reaction time was 48 h) from alkylazaarene **1.91b** (114 mg, 0.50 mmol) and nitroalkene **1.65c**^[66] (116 mg, 0.75 mmol) and purified by



column chromatography (2→16% acetone/hexane) to give a brown gum (138 mg, 78%). R_f 0.20 (20% acetone/hexane); $[\alpha]_D^{20}$ -55 (c 1.00, CHCl_3); IR (film) 1601, 1558, 1555, 1524 (NO_2), 1379, 1350 (NO_2), 858, 758, 725, 702 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.49 (1H, d, J = 2.6 Hz, ArH), 8.19 (1H, dd, J = 8.5, 2.7 Hz, ArH), 7.32 (1H, t, J = 3.2 Hz, ArH), 7.15-7.10 (3H, m, ArH), 7.01 (2H, d, J = 3.5 Hz, ArH), 6.85 (1H, dd, J = 8.5, 0.6 Hz, ArH), 6.79-6.75 (2H, m, ArH), 4.56-4.43 (3H, m, CH_2NO_2 , CHCH_2N), 3.55-3.50 (1H, m, CHCH_2Ph), 3.07 (1H, dd, J = 13.4, 3.9 Hz, CH_2Ph), 2.92 (1H, dd, J = 13.4, 11.0 Hz, CH_2Ph); ^{13}C NMR (125.8 MHz, CDCl_3) δ 166.8 (C), 145.3 (CH), 143.0 (C), 140.7 (C), 138.2 (C), 131.0 (CH), 128.6 (2 x CH), 128.4 (2 x CH), 127.3 (CH), 127.0 (CH), 126.6 (CH), 125.4 (CH), 125.1 (CH), 79.2 (CH_2), 54.4 (CH), 43.6 (CH), 40.3 (CH_2); HRMS (ESI +ve) Exact mass calculated for $\text{C}_{21}\text{H}_{24}\text{N}_3\text{O}_5$ $[\text{M}+\text{H}]^+$: 383.0934, found: 383.0933. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (80:20 hexane:*i*-PrOH, 2.0 mL/min, 230 nm, 25 °C); t_r (major) = 4.4 min, t_r (minor): 4.8 min, 95% ee.



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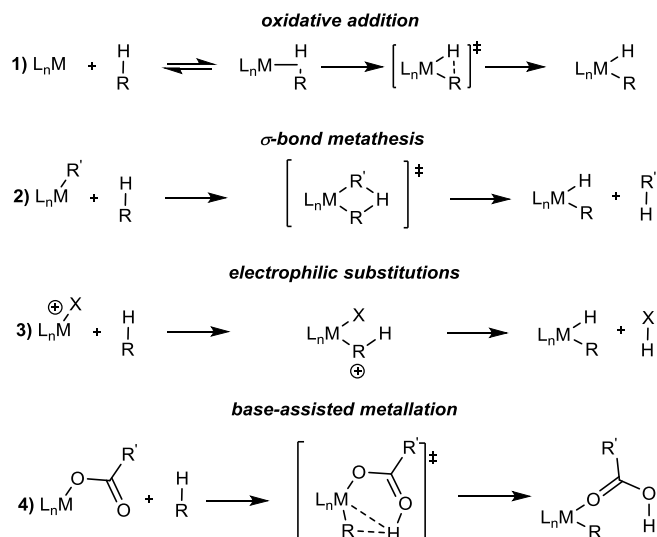


2. SYNTHESIS OF SPIROCYCLIC ENONES VIA RH(III)-CATALYSED C–H FUNCTIONALISATION

2.1 INTRODUCTION

Transition metal-catalysed C–H functionalisation reactions have attracted much attention among many research groups over the last couple of decades, as they provide shorter synthetic routes for delivering complex molecules. Moreover, this strategy in comparison with classical C–C cross-coupling reactions, such as Suzuki-Miyaura,^[1] Stille,^[2] Kumada^[3] and Negishi^[4] reactions, enables formation of new C–C, C–X bonds (X = heteroatom) without preactivating substrates. From an atom- and step-economical point of view this is highly desirable. Furthermore, generation of toxic by-product waste is reduced, thus making this process more environmentally friendly.

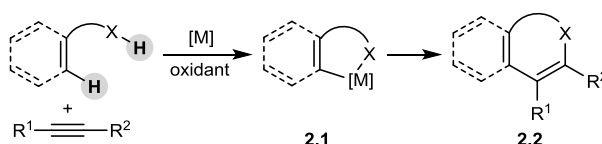
To understand the functionalisation of the “inert” C–H bond, mechanistic studies have been conducted and showed that depending on the metal character, four types of metallation mechanisms can be distinguished: oxidative addition, σ -bond metathesis, electrophilic substitution and base-assisted metallation (Scheme 2.1).^[5]



Scheme 2.1: Four typical mechanisms for C–H metallation.^[5]



The base-assisted metallation mechanism has been widely studied in the oxidative heteroatom-directed functionalisation of aromatic C–H bonds in the reactions with alkynes and 1,3-enynes. In particular, reactions catalysed by Rh,^[6] Ru^[7] and Pd^[8] catalysts will be presented in this part of the thesis as they stand out for functional group tolerance. The oxidative heteroatom-directed approach itself is one of the most promising areas of C–H functionalisation chemistry, where the metal centre of the catalyst coordinates to the built-in directing group of the substrate to functionalise a C(sp²)–H bond and form metalacycle **2.1** (Scheme 2.2).^[9] Subsequent coordination and migratory insertion of the alkyne (or 1,3-enyne) followed by C–X (X = heteroatom) reductive elimination delivers hetero- or carbocyclic product **2.2**. Furthermore, as the C–H bond acts as a poor Lewis base, the introduction of a substituent on the reagent, can alter its character and thus, make this process site-selective.^[10] The directing groups used in these reactions are commonly known functional groups such as carboxylic acids, naphthols and imines.



Scheme 2.2: Existing alkyne oxidative annulations by X-H/C(sp²)-H bond cleavage

Due to the high interest within our group, in regards to oxidative heteroatom-directed C(sp²)–H functionalisation reactions with alkynes, attempts have been made to broaden the substrate scope in this area. Thus, the recent work on the use of 2-alkenylphenols in the oxidative annulation reactions with alkynes and 1,3-enynes to form spirocyclic enones will be described here. However, a brief overview, of *N*- and *O*-containing directing groups, based on existing literature, will be presented first.

2.2 NITROGEN-CONTAINING DIRECTING GROUPS

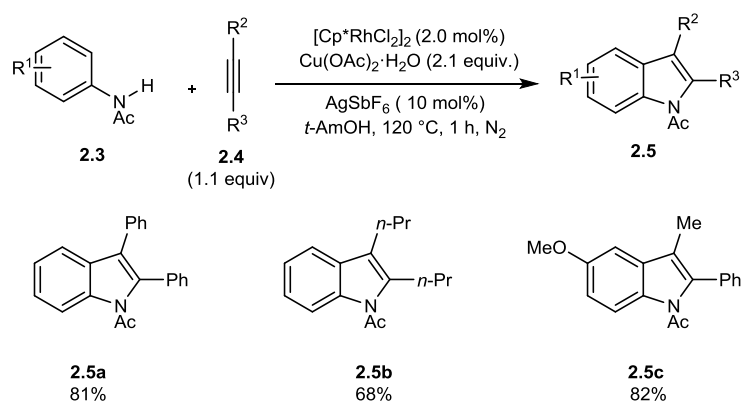
This section highlights some examples of various *N*-containing directing groups which have been widely studied in transition-metal catalysed alkyne oxidative annulations. The Lewis basic character of the directing groups is due to the lone pair



positioned at the nitrogen atom that coordinates to the metal centre and promotes a substrate-catalyst interaction leading to site-selective C–H bond cleavage. Subsequent alkyne migratory insertion, followed by reductive elimination, gives the annulated product.

2.2.1 AMIDES

The first Rh-catalysed oxidative annulation reaction of alkynes **2.4** with acetanilides **2.3** to deliver *N*-acetyl indoles **2.5** was reported by Fagnou in 2008.^[11] The optimal conditions were found to be 2.5 mol% [Cp*RhCl₂]₂ catalyst, 2.0 equivalents Cu(OAc)₂·H₂O, 10 mol% AgSbF₆ in *t*-AmOH at 120 °C (Scheme 2.3). The products were obtained in moderate to high yields and the reaction was also tolerant towards alkyl/aryl alkynes.



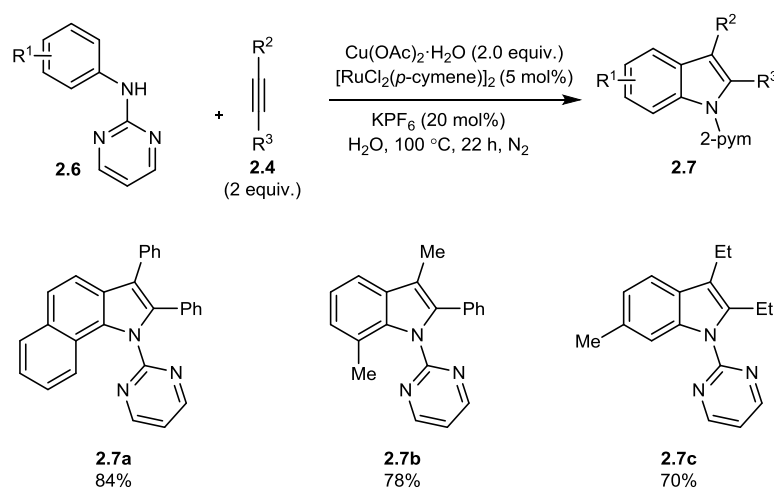
Scheme 2.3: Indole synthesis *via* Rh-catalysed annulation of alkynes with acetanilides.^[11]

This methodology was later modified by the introduction of [Cp*Rh(MeCN)₃][SbF₆]₂ complex and air as a co-oxidant to remove the need for the addition of a silver salt and to reduce the super-stoichiometric amount of Cu(OAc)₂·H₂O oxidant. These reaction conditions were then applied to the synthesis of pyrroles.^[12] Later that year, the same group showed that the synthesis of various unsymmetrical 2,3-aliphatic-substituted indoles and pyrroles can be achieved in the reaction with 1,3-enynes rather than alkynes.^[13]



2.2.2 PROTECTED ANILINES

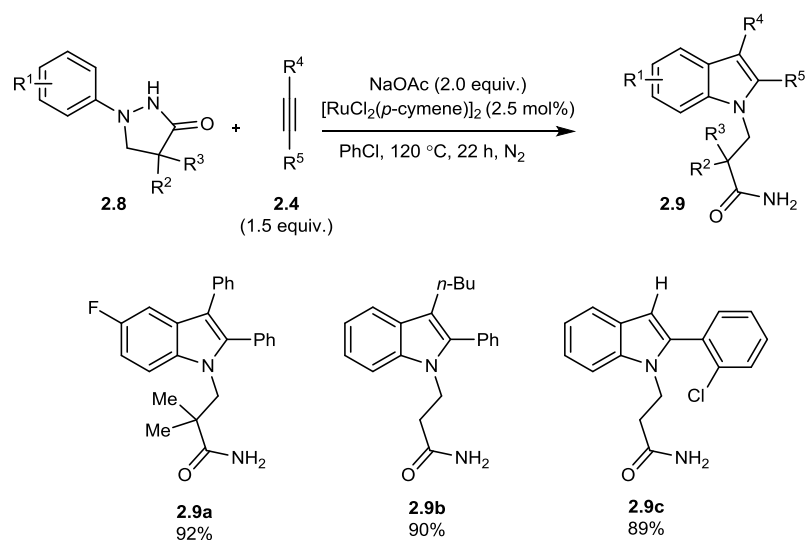
In 2012, Ackermann and co-workers reported the Ru-catalysed reaction of 2-pyrimidine protected anilines **2.6** with alkynes **2.4** which resulted in the formation of various substituted indole products **2.7** (Scheme 2.4).^[14] The active cationic Ru(II) complex, with weakly coordinating anion PF_6^- , was generated from $[\text{RuCl}_2(p\text{-cymene})]_2$ and KPF_6 . The efficiency of the reaction was high and delivered a broad range of the indole products **2.7**. Diaryl, dialkyl and unsymmetrical alkenes were well tolerated. Moreover, the reaction was conducted in water as a sustainable solvent.



Scheme 2.4: Ru-catalysed oxidative annulation of protected anilines with alkynes.^[14]

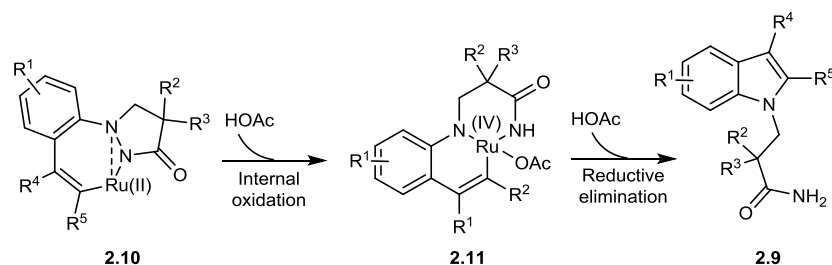
An alternative approach for the synthesis of *N*-substituted indoles was presented by the group of Huang.^[15] They envisioned that introduction of a functional group that would serve as a directing group and in-built oxidant, would make this reaction redox-neutral. Further investigation revealed that under Ru(II) catalysis pyrazolidin-2-ones **2.8** were good substrates for the oxidative annulation with alkynes **2.4** and gave the final products **2.9** in high yields and with high levels of regioselectivity (Scheme 2.5).





Scheme 2.5: Ru-catalysed oxidative annulation of pyrazolidin-2-ones with alkynes.^[15]

The proposed mechanism of this reaction is slightly different from the general one, previously described for the Ru-catalysed oxidative annulation processes. After acetate-assisted cyclometallation and alkyne insertion to give intermediate **2.10**, the Ru(II) complex is further oxidised to Ru(IV) **2.11** by N–N bond cleavage. The release of the final product **2.9** occurs after reductive elimination (Scheme 2.6).

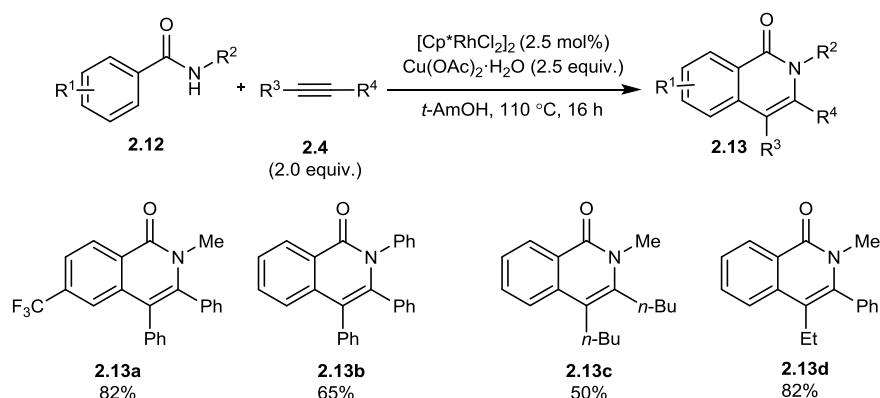


Scheme 2.6: Proposed mechanism of the indole synthesis *via* N–N bond cleavage.^[16]

Based on pioneering work by Fagnou in 2008,^[11] regarding Rh-catalysed indole synthesis using acetanilides, the Rovis group proposed using amides **2.12** as a directing group for delivering isoquinolones **2.13** *via* C–H bond cleavage and subsequent C–N bond formation (Scheme 2.7).^[17] In general, this reaction worked smoothly in the presence of [Cp*RhCl₂]₂ (2.5 mol%) and a super-stoichiometric amount of Cu(OAc)₂·H₂O oxidant in *t*-AmOH at 110 °C. A range of symmetrical



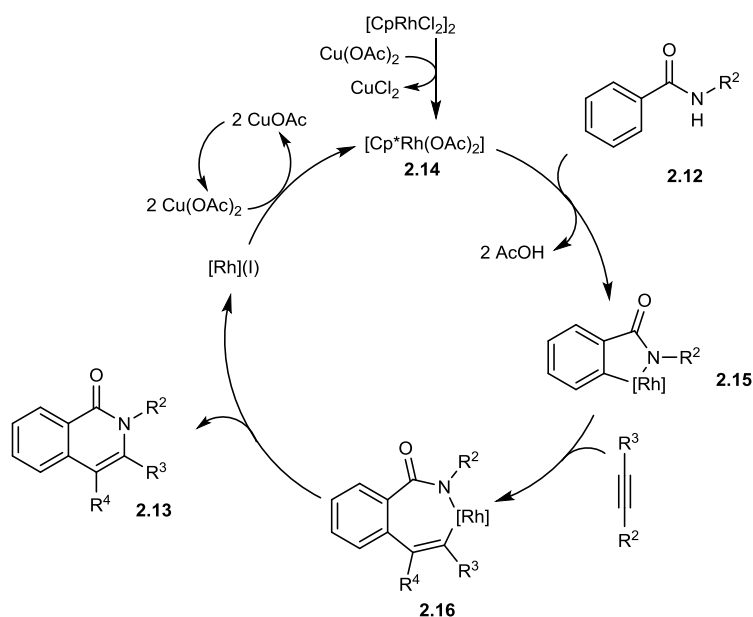
aryl and alkyl alkynes as well as unsymmetrical variants, gave the final isoquinolones **2.13** in moderate to high yields. This process also tolerated various substituents at the nitrogen atom and aryl ring of the amide (**2.13a** and **2.13b**). A year later a less expensive $[\text{RuCl}_2(p\text{-cymene})]_2$ catalyst for the oxidative annulation of alkynes with amides was investigated and published by Ackermann and co-workers.^[18] The efficacy of this process was as good as the Rh-catalysed reaction.



Scheme 2.7: Synthesis of isoquinolones *via* Rh-catalysed oxidative annulation of alkynes.^[17]

The mechanism proposed by Rovis is shown below (Scheme 2.8). The success of this reaction is due to the heteroatom assistance, in this case the nitrogen atom of the amide group. Coordination of the amide to the active catalyst $[\text{Cp}^*\text{Rh}(\text{OAc})_2]$ **2.14** facilitates site-selective $\text{C}(\text{sp}^2)\text{-H}$ functionalisation to form rhodacycle **2.15**. This carbometallation proceeds with a carboxylate assistance allowing then migratory insertion of an alkyne to form the 7-membered rhodacycle **2.16**. Reductive elimination releases the final product **2.13** and Rh(I) catalyst which is oxidised with $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ to regenerate the active catalyst species **2.14** (Scheme 2.8).

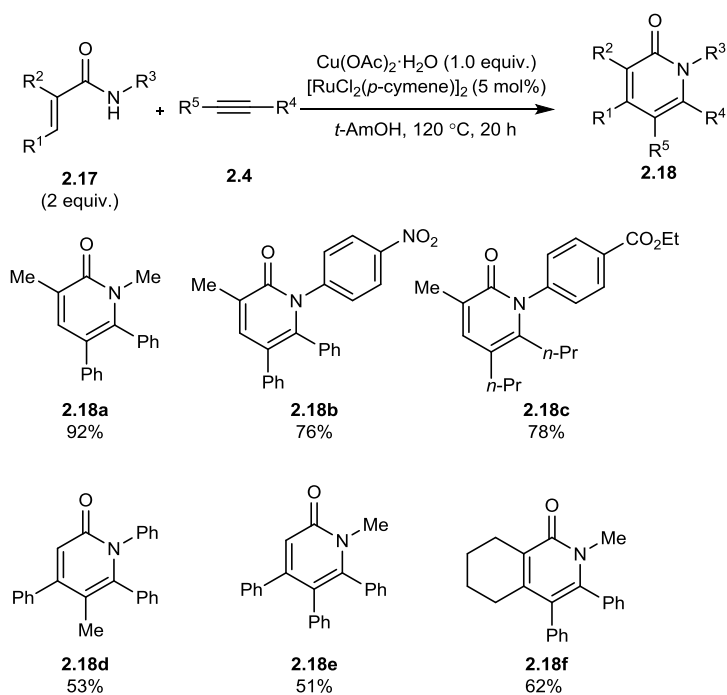




Scheme 2.8: Rh-catalysed oxidative annulation of alkynes to form isoquinolones.^[17]

Further exploration of substrate scope by Ackermann and co-workers showed that the reaction of various acrylamides **2.17** with alkynes **2.4** under ruthenium catalysis, with a $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ oxidant in *t*-AmOH at 120 °C can provide a range of 2-pyridones **2.18** (Scheme 2.9).^[19] In comparison with the Rh-catalyst, previously described by Li,^[20] this ruthenium catalysed reaction did not require superstoichiometric amounts of the external oxidant and was efficient for dialkyl substituted alkynes (which afforded a complicated mixture of compounds in the corresponding Rh-catalysed process). The addition of alkyl/aryl-substituted alkynes was site-selective regardless of the nature of the substituent at the *N*-amide position (poor selectivity in case of Rh process).



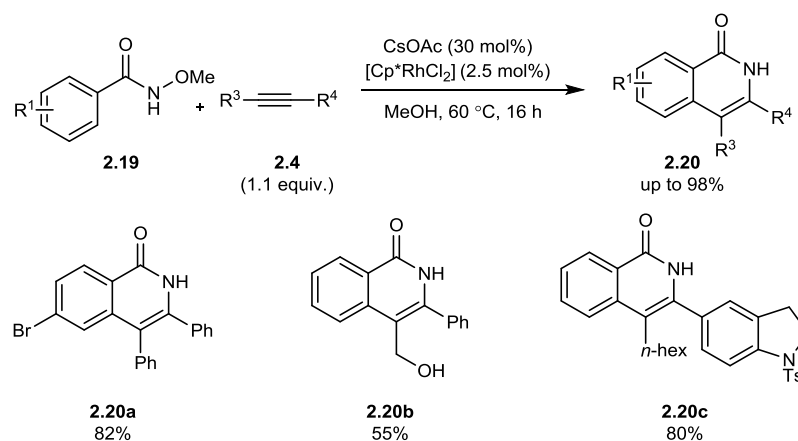


Scheme 2.9: Synthesis of 2-pyridones under Ru-catalysis.^[19]

2.2.3 BENZHYDROXAMIC ACIDS

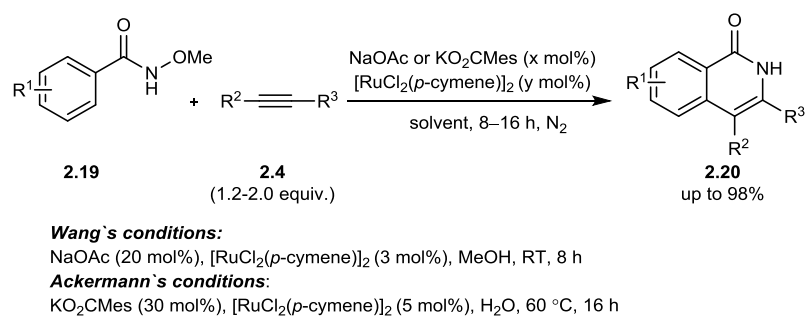
In 2010, Fagnou and co-workers reported an intermolecular process that delivered the isoquinolone products **2.20** *via* Rh-catalysed annulation of benzhydroxamic acids **2.19** with alkynes **2.4** (Scheme 2.10).^[21] The reaction worked smoothly without the addition of an external oxidant. The active catalyst was regenerated *via* N–O bond cleavage present in the substrate as a built-in oxidant. In general, electron-withdrawing and donating groups on the aryl ring were well tolerated as well as symmetrical aryl or unsymmetrical alkyl/aryl alkynes. The reaction did not work for terminal alkynes, which gave the homocoupled by product instead.





Scheme 2.10: Rh-catalysed oxidative annulation of isoquinolones.^[21]

Following these observations, an alternative method for the synthesis of isoquinolones **2.20** via C–H activation using an oxidising methoxy group was proposed by the groups of Li and Wang^[22] and Ackermann.^[23] Wang's conditions required running the reaction of benzhydroxamic acids **2.19** with alkynes **2.4** with 3 mol% $[\text{RuCl}_2(p\text{-cymene})]_2$ catalyst and 20 mol% NaOAc in methanol at room temperature. The addition of NaOAc was required as the acetate anion takes part in the cyclometallation step and regenerates the catalyst. Notably, Ackermann showed that a catalytic system consisting of 2.5 mol% $[\text{RuCl}_2(p\text{-cymene})]_2$, 30 mol% of KO_2CMes as a carboxylate source, in water was also highly effective (Scheme 2.11).

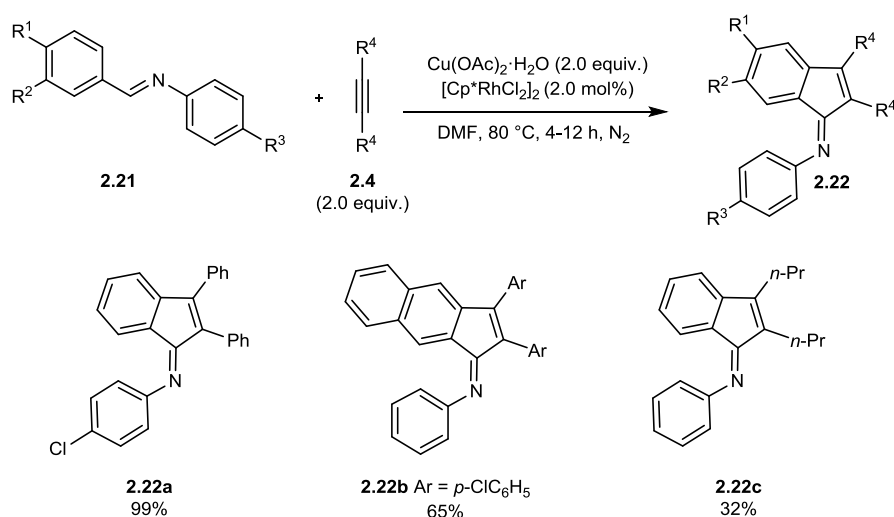


Scheme 2.11: Oxidising directing group in Ru-catalysed annulations with alkynes.^{[22],[23]}



2.2.4 IMINES

Satoh and Miura had also shown that *N*-benzylideneanilines **2.21** can react with internal alkynes **2.4** using 2 mol% $[\text{Cp}^*\text{RhCl}_2]_2$ and 2.0 equivalents $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in DMF at 80 °C under N_2 to give indenone imines **2.22** (Scheme 2.12).^[24] With respect to substrate scope various *N*-benzylideneanilines were tolerated regardless of the electronic character of the substituent. However, an *N*-alkylimine, e.g. benzylidene *N*-*tert*-butylamine, was recovered under optimised reaction conditions. Symmetrical diaryl alkynes gave good to high yields (compounds **2.22a** and **2.22b**), whereas the reaction with dialkyl, 4-octyne yielded the indenone product **2.22c** in only 32%. The terminal alkynes phenylacetylene underwent dimerisation forming diphenylbutadiyne instead.

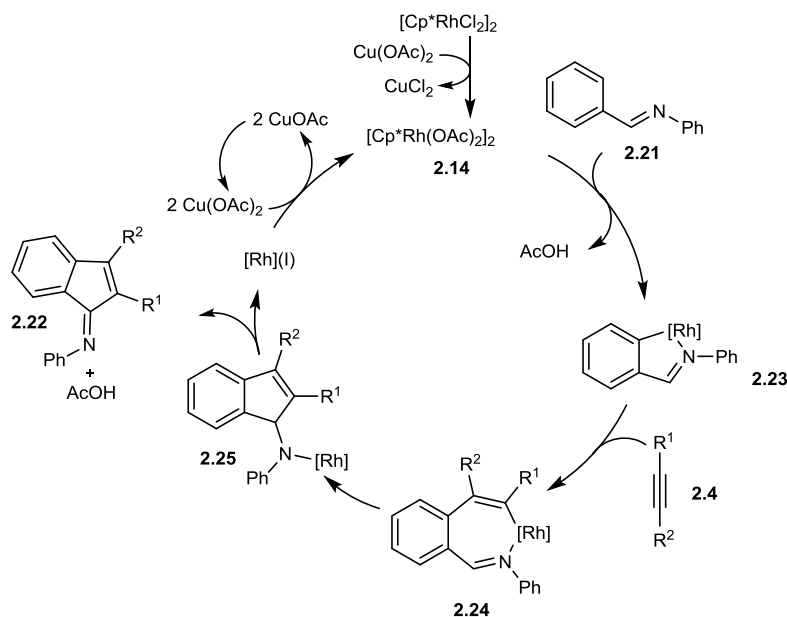


Scheme 2.12: Rh-catalysed indenone imine formation.^[24]

A plausible mechanism in the reaction of *N*-benzylideneaniline with alkynes is highlighted in Scheme 2.13. Formation of the active catalyst **2.14** via ligand exchange with $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ occurs first. Coordination of the catalyst to the nitrogen atom of the imine facilitates the acetate-assisted C–H bond cleavage to form a five-membered rhodacycle **2.23**. Coordination and migratory insertion of the alkyne **2.4** forms the seven-membered ring intermediate **2.24** which undergoes intramolecular insertion of the imino moiety to form **2.25**. β -Hydrogen elimination

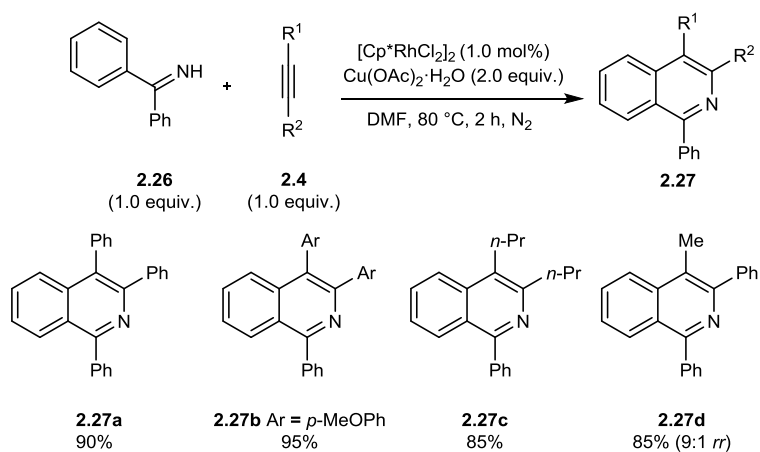


forms the indenone imine final product **2.22** and the Rh(I) catalyst is reoxidised to Rh(III).



Scheme 2.13: A plausible mechanism for the indenone imine formation.^[24]

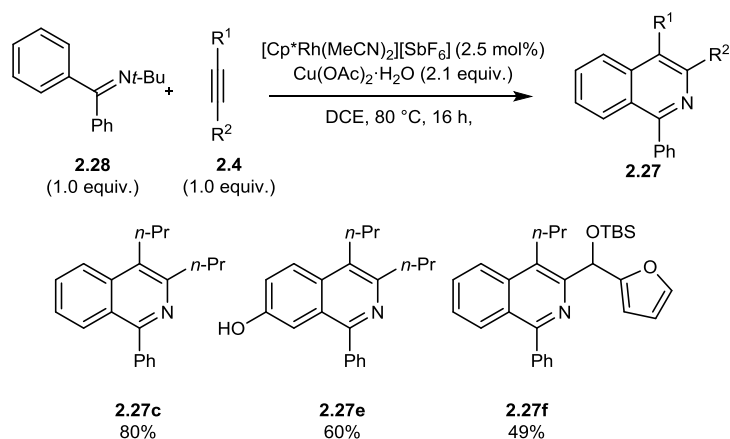
Furthermore, under similar conditions benzophenone imine **2.26** reacted with internal alkynes **2.4** to give isoquinoline product **2.27** (Scheme 2.14). Dialkyl, diaryl as well as the unsymmetrical alkynes were well tolerated in this reaction giving high yields of the final product.



Scheme 2.14: Synthesis of isoquinolines.^[24]



Simultaneously, Guimode and Fagnou showed that isoquinolines **2.27** can be obtained in the reaction of *N-tert*-butylbenzaldimine **2.28** with internal alkynes **2.4** in the presence of 2.5 mol% [Cp*Rh(MeCN)₂][SbF₆]₂, 2.1 equivalents Cu(OAc)₂·H₂O in DCE at reflux (Scheme 2.15).^[25] This reaction worked well for dialkyl alkynes; however there are no examples for diaryl alkynes. Unsymmetrical alkynes gave the final product with up to >19:1 regioselectivity. Terminal alkynes were not good coupling partners, giving the alkyne dimerised product instead.



Scheme 2.15: Rh-catalysed isoquinoline **2.27** formation.^[25]

2.3 O-BASED DIRECTING GROUPS

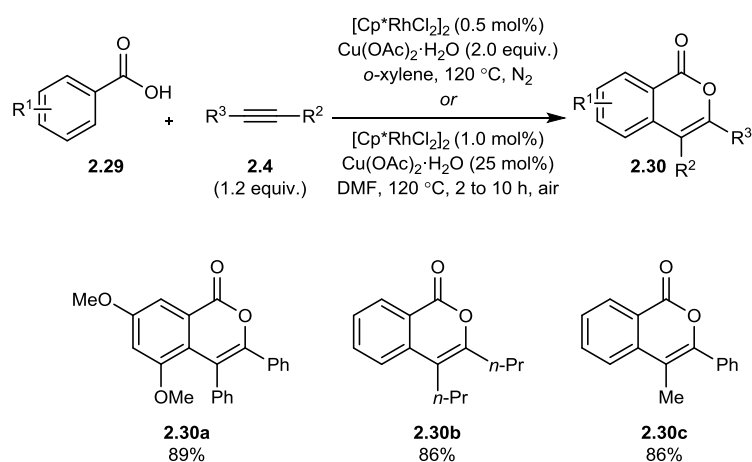
In the previous section it was shown that various *N*-containing hetero- and carbocycles could be easily prepared by the use of *N*-coordinating directing groups in the oxidative coupling reactions with alkynes. Catalytic, direct C–H functionalisation of substrates containing *O*-based directing groups has also received a lot of attention in the last decade due to the formation of biologically significant molecules. Below, commonly used functional groups in this oxidative annulation process are described.

2.3.1 CARBOXYLIC ACIDS

One of the pioneering studies, describing an alkyne oxidative annulation process, was reported by the group of Satoh and Miura in 2007.^{[26],[27]} They showed that the employment of benzoic acids **2.29** and internal alkynes **2.4** can provide a wide range of isocoumarin products **2.30**, a motif present in many biologically active molecules



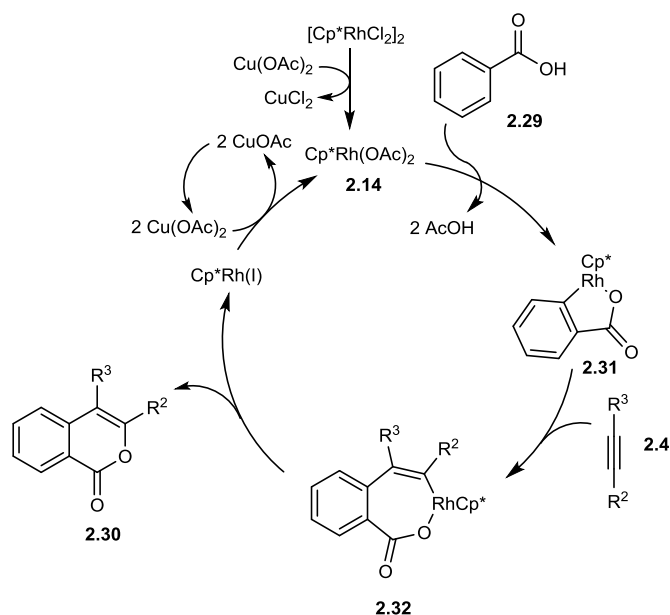
and natural products.^[28] Various Rh-based catalysts such as $\text{RhCl}_3 \cdot \text{H}_2\text{O}$, $\text{Rh}(\text{acac})$, $[\text{RhCl}(\text{cod})_2]_2$ or $[\text{RhCl}(\text{C}_2\text{H}_2)]_2$ (acac = acetylacetonate, cod = 1,5-cyclooctadiene) were not efficient for this transformation. However, the optimised reaction conditions consisted of 0.5 mol% $[\text{Cp}^*\text{RhCl}_2]_2$ catalyst and 2.0 equivalents of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ oxidant in *o*-xylene at 120 °C and provided the final products with satisfying yields and high regioselectivity (Scheme 2.16). This procedure worked smoothly for various internal alkynes but was not effective for terminal or silyl-protected alkynes. Furthermore, running the reaction with a catalytic amount of oxidant under an air atmosphere was also efficient in delivering isocoumarins.



Scheme 2.16: Formation of isocoumarins under Rh-catalysis.^{[26],[27]}

During the reaction, the carboxylate oxygen chelates to the metal centre and facilitates the site-selective $\text{C}(\text{sp}^2)\text{--H}$ bond cleavage, *via* acetate assistance, to form a five-membered rhodacycle **2.31** (Scheme 2.17). Then, a migratory alkyne insertion generates a seven-membered rhodacycle **2.32** which undergoes reductive elimination to form the isocoumarin product **2.30**. Oxidation of the catalyst with $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ regenerates the active catalytic species.

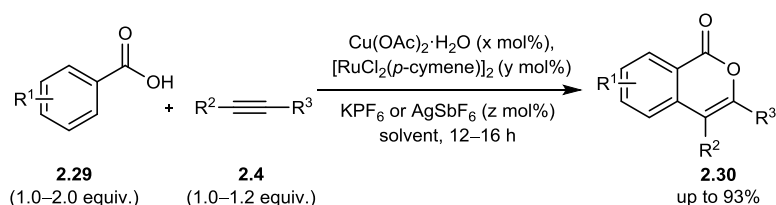




Scheme 2.17: Proposed mechanism for isocoumarin formation.^{[26],[27]}

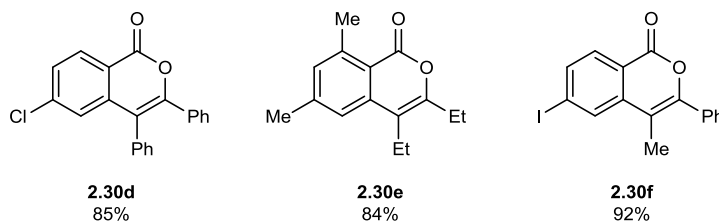
Despite the versatility of both methods, the cost of the catalyst and low abundance of the metal drove other groups to find less expensive approaches. In 2012, the groups of Ackermann^[29] and Jeganmohan^[30] published independently an alternative synthesis of isocoumarins **2.30** *via* the cationic Ru(II)-catalysed oxidative annulation of aromatic acids **2.29** and alkynes **2.4** (Scheme 2.18). Furthermore, they both showed that the reaction proceeds smoothly with symmetrical dialkyl/diaryl alkynes and was highly regioselective for alkyl/aryl alkynes. The substrate scope with regards to aryl carboxylic acids and their derivatives was also investigated. Both groups used different silver salts for the formation of the active cationic Ru(II) complex. In Ackermann's studies AgPF₆ was used, while Jeganmohan's conditions required the addition of AgSbF₆. The latter counterion played an important role in controlling the regioselectivity and suppressing the formation of decarboxylated naphthalene by-product.





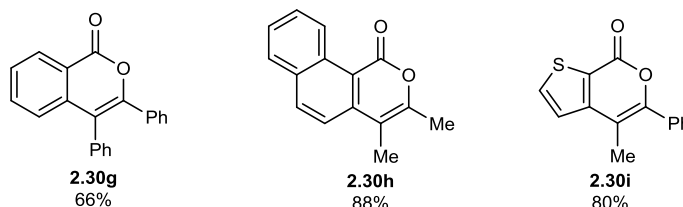
Ackermann's conditions:

$\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}$ (2.0 equiv.), KPF_6 (20 mol%), $[\text{RuCl}_2(\text{p-cymene})]_2$ (2.5 mol%), *t*-AmOH, 120 °C, 16 h



Jeganmohan's conditions:

$\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}$ (10 mol%), AgSbF_6 (20 mol%), $[\text{RuCl}_2(\text{p-cymene})]_2$ (2.0 mol%), DCE, 100 °C, 12 h



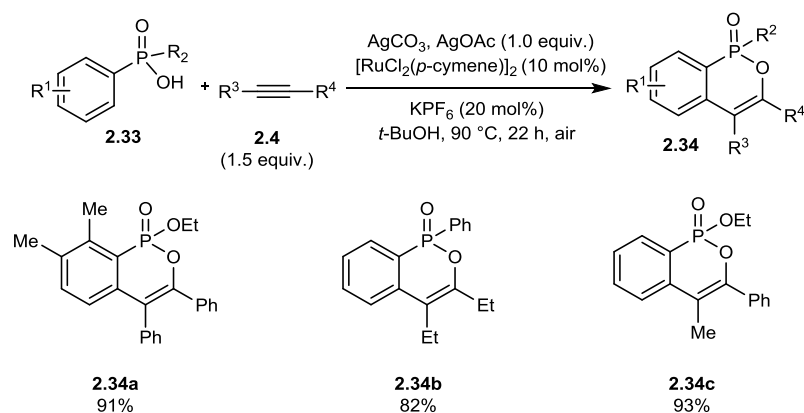
Scheme 2.18: Ru-catalysed oxidative annulation of aryl carboxylic acids with alkynes.^{[29],[30]}

2.3.1.1 Phosphinic acids and phosphonic monoesters

Attention has also been given to phosphinic acids and their monoesters, which have been used to form biologically active phosphaisocoumarines.^[31] For example, in 2013 the group of Satoh and Miura,^[32] as well as the Lee group^[33] reported independently, the Rh-catalysed oxidative annulation of alkynes directed by phosphonic acids and their monoesters. Subsequently, a Ru-catalysed alternative process for the formation of these phosphorus heterocyclic compounds **2.34** was also developed by the Lee group (Scheme 2.19).^[34] This reaction worked using a Ru(II)-catalyst (10 mol%) with a combination of two oxidising agents, AgCO_3 and AgOAc (1 equivalent of each). Aryl phosphonic acids and their monoester derivatives possessing electron-donating or withdrawing groups were cyclised with a range of diaryl, dialkyl and aryl/alkyl alkynes giving high yields (**2.34a–c**). The mechanism is thought to be similar to that for benzoic acids where the reaction goes through



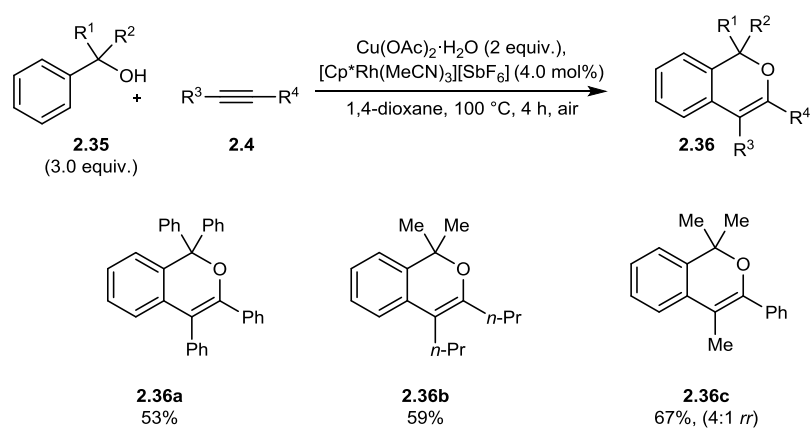
hydroxyl chelation to the Ru metal centre which allows the C–H activation/functionalisation. C–O bond formation *via* reductive elimination releases the phosphaisocoumarin product.



Scheme 2.19: Ru-catalysed synthesis of phosphaisocoumarins by the Lee group.^[34]

2.3.2 BENZYLIC ALCOHOLS

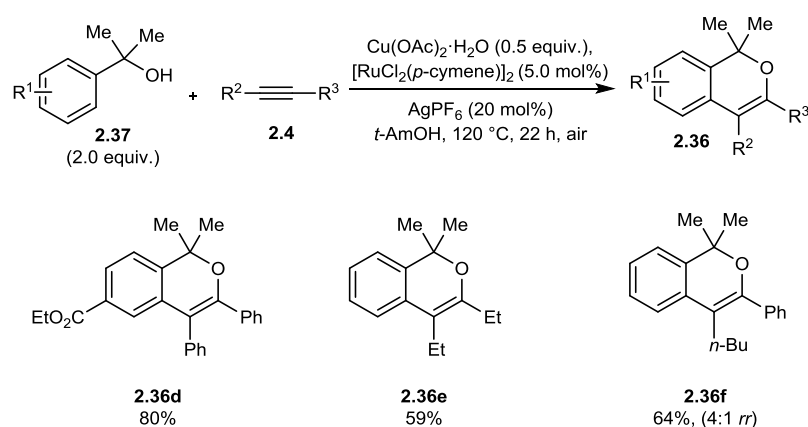
The group of Satoh and Miura investigated a Rh-catalysed oxidative annulation reaction of α,α -disubstituted benzylic alcohols **2.35** with alkynes **2.4**.^[35] In 2011, they showed that the catalytic system of 4 mol% $[\text{Cp}^*\text{Rh}(\text{MeCN})_3][\text{SbF}_6]_2$, 2 equivalents $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in 1,4-dioxane at reflux was effective for the synthesis of isochromenes **2.36** (Scheme 2.20).



Scheme 2.20: Synthesis of isochromenes under Rh-catalysis.^[35]



Following the development of this methodology, the group of Ackermann presented their work on the Ru-catalysed oxidative annulation of α,α -dialkyl substituted benzylic alcohols **2.37** with alkynes **2.4** (Scheme 2.21).^[36] During the optimisation of the reaction conditions, it was found that the loading of the external oxidant, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, could be lowered to 0.5 equivalent in the presence of air as a co-oxidant. Overall, diaryl and dialkyl alkynes were tolerated (compounds **2.36d** and **2.36e**), with moderate regioselectivity for unsymmetrical alkynes with the major product possessing the aryl group proximal to oxygen substituent (**2.36f**). Unfortunately, terminal alkynes were not successful coupling partners for this transformation.



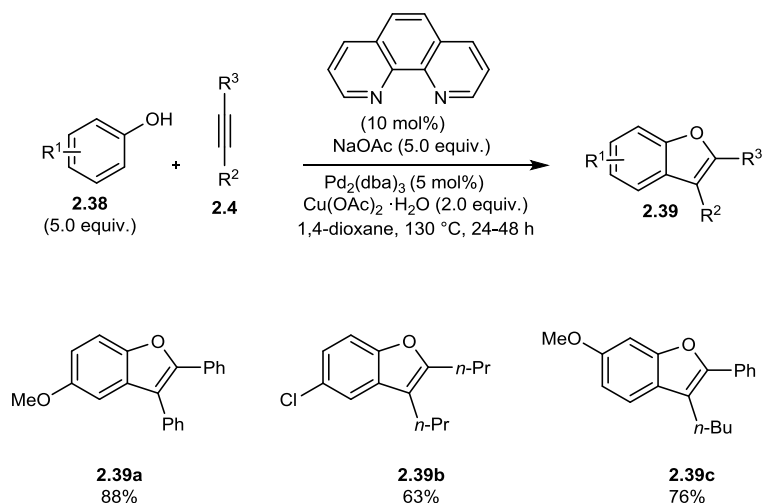
Scheme 2.21: Ru-catalysed oxidative annulation of benzylic alcohols with alkynes.^[36]

2.3.3 PHENOLS

The utility of commercially available phenols and their derivatives in transition-metal catalysed oxidative annulation reactions of alkynes has been of high interests. The group of Sahoo and co-workers demonstrated the synthesis of 2,3-disubstituted benzofurans **2.39** in the reaction of phenols **2.38** with alkynes **2.4**.^[37] The highest yields were obtained using the combination of $[\text{Pd}_2(\text{dba})_3]$ catalyst, 1,10-phenanthroline ligand, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and NaOAc (Scheme 2.22). Simultaneously, the group of Shi also achieved the direct synthesis of benzofurans;^[38] however, the Rh(III)/Cu(II)-catalysed process was not efficient for dialkyl or alkylaryl alkynes in comparison to Sahoo's palladium conditions (**2.39b** and **2.39c**). Overall, both of



these sets of results are significant because they prove the ability of phenols to form homocoupled products in the presence of oxidants.^{[39],[40]}



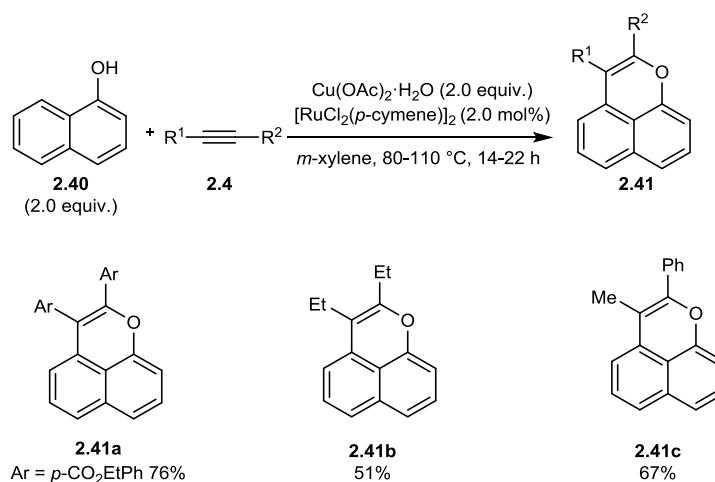
Scheme 2.22: Pd-catalysed oxidative annulation of alkynes with phenols.^[37]

2.3.4 NAPHTHOLS

1-Naphthols and their analogues have been used in oxidative annulation reactions with alkynes and was reported in 2010 by Satoh and Miura.^[41] In their elegant work they showed that with $[\text{Cp}^*\text{RhCl}_2]_2$ catalyst and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ oxidant, the C–H bond cleavage occurred at the *peri* position of the 1-naphthol to give the fused polycyclic product. This method proved to be successful only for symmetrical alkynes.

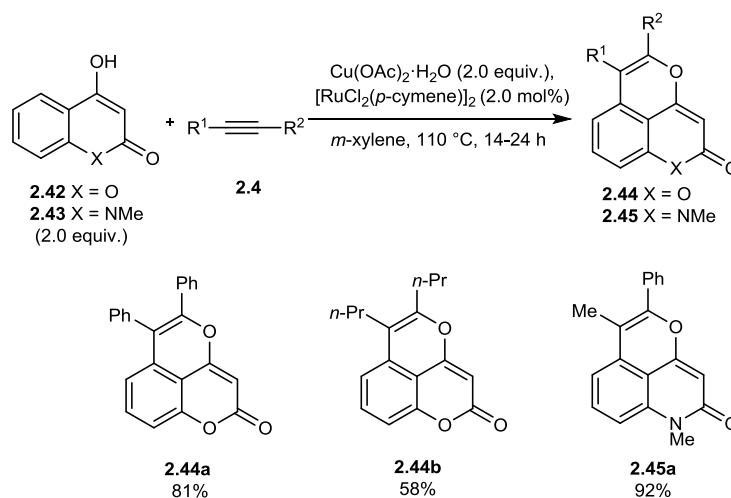
An alternative approach for the synthesis of naphthalpyrans **2.41** was presented by Ackermann and co-workers in 2012.^[42] In the presence of 2.0 mol% $[\text{RuCl}_2(p\text{-cymene})]_2$ catalyst, 2.0 equivalents $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, various 1-naphthols **2.40** and alkynes **2.4** delivered ample scope of naphthalpyrans **2.41** (Scheme 2.23). This method was efficient for a range of dialkyl, diaryl and alkyl/aryl alkynes.





Scheme 2.23: Ru-catalysed oxidative annulation of 1-naphthols **2.40** and alkynes **2.4**.^[42]

This catalytic system was also tested in the reaction of various alkynes **2.4** with 4-hydroxycoumarin **2.42** and quinoline-2-one **2.43** giving the final products **2.43** or **2.44** in high yields. (Scheme 2.24). This process delivered a novel range of fluorescent pyrans *via* high regio-, site- and chemo-selective C–H/C–O bond functionalisation.

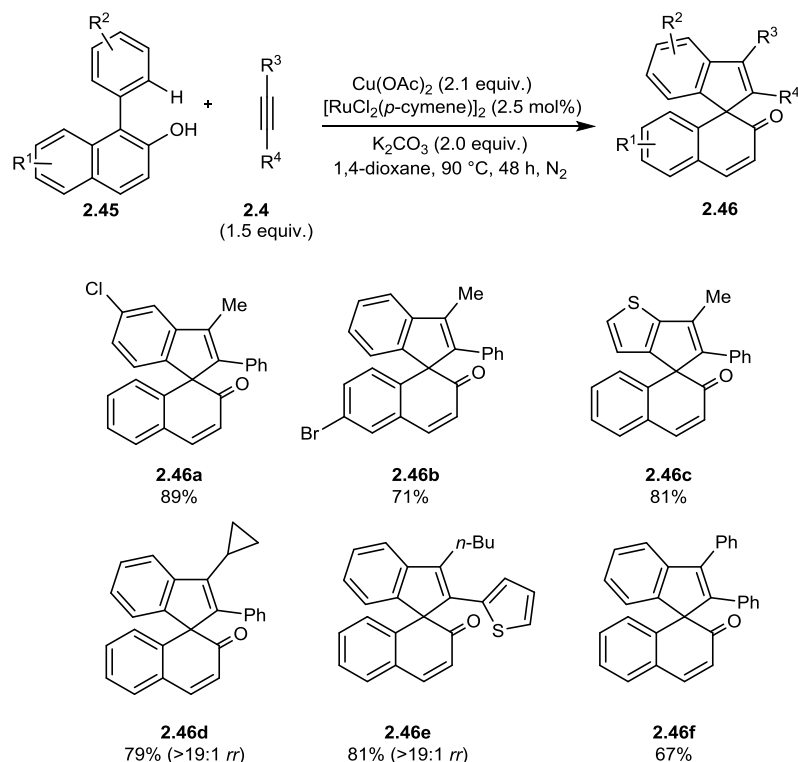


Scheme 2.24: Ru-catalysed synthesis of fluorescent pyrans.^[42]

Recently, the group of Luan and co-workers reported the formation of spirocyclic products **2.46** *via* a C–H activation-dearomatisation tandem process of 1-(hetero)aryl-2-naphthols **2.45** with alkynes **2.4**.^[43] The optimum conditions were



found to be a catalyst system consisting of 2.5 mol% $[(\text{RuCl}_2(p\text{-cymene}))_2]$, 2.1 equivalents $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, and 2.0 equivalents of K_2CO_3 in 1,4-dioxane at 90 °C for 48 h (Scheme 2.25). In terms of substrate scope, the aryl and naphthol rings could be substituted at various positions and gave the annulated final products in high yields (products **2.46a** and **2.46b**). Changing the substituent from aryl to a heteroaryl system at the 1-position of the naphthol was also successful (81%, compound **2.46c**). Overall, the final products were obtained as single regioisomers or >19:1 mixtures when unsymmetrical alkynes were employed (**2.46a–d**). Symmetrical alkynes, such as diphenylacetylene, were tolerated (**2.46f**); however in the intermolecular competition experiment, it was noticed that electron-rich alkynes delivered the final product in better yield.



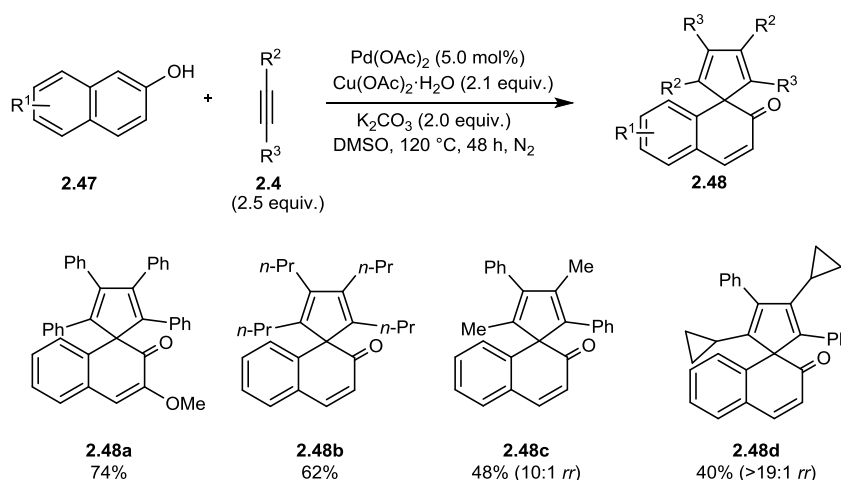
Scheme 2.25: Ru-catalysed spiroannulation of (hetero)aryl naphthols.^[43]

This Ru-catalysed system was efficient for 1-aryl-2-naphthols; however the optimised conditions, as well as other screened Rh- and Pd-based catalysts, were not effective for phenol-derived substrates. That could indicate that the energetic penalty



of dearomatisation of the phenol substrate is more challenging in comparison with 2-naphhtols. (Studies utilising phenols and their derivatives in oxidative annulation directed C–H functionalisation reactions with alkynes can be found in the Research and Discussion Part).

Luan and co-workers also showed that 2-naphhtols **2.47** and 2.5 equivalents of alkynes **2.4** in the presence of Pd(OAc)₂ catalyst and Cu(OAc)₂·H₂O oxidant can form a range of spirocyclic compounds *via* [2 + 2 + 1] oxidative annulation (Scheme 2.26).^[44] Other transition-metal catalysts, commonly used in C–H functionalisation reactions, based on Rh, Rh or Pd, were not effective for this transformation. Overall, various substituents introduced at the 2-naphthol ring were tolerated regardless of their electronic character. Dialkyl, di(hetero)aryl and unsymmetrical alkynes underwent spiroannulation giving good to high yields and in high regioselectivity.

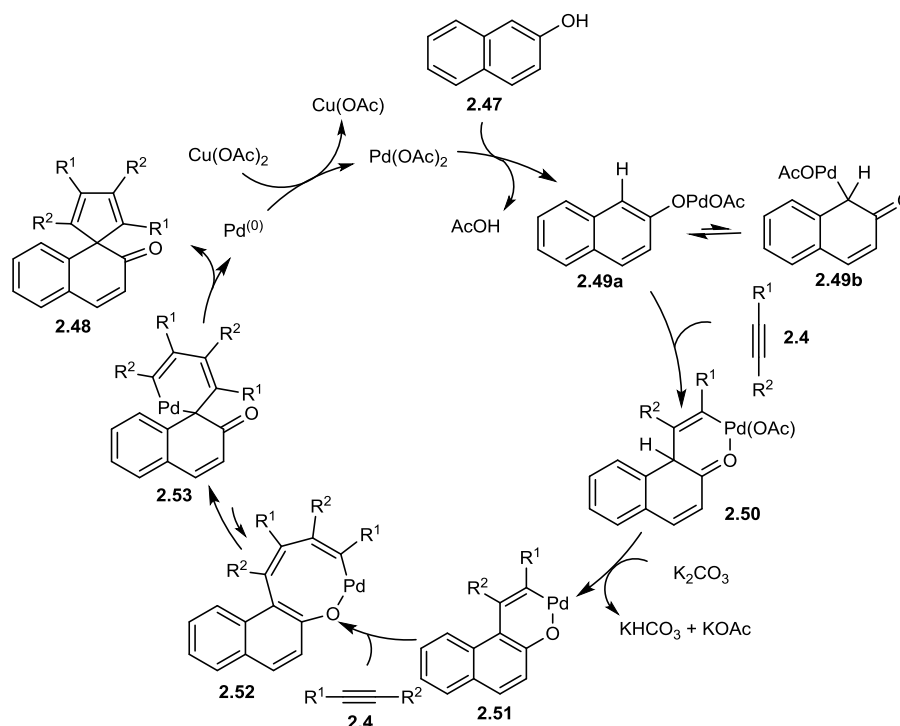


Scheme 2.26: Pd-catalysed one-pot synthesis of spiroannulated 2-naphthols.^[44]

A mechanism of this double alkyne addition was also proposed (Scheme 2.27). Deprotonation of 2-naphthol substrate **2.47** by Pd(OAc)₂ forms the palladiumphenoxide species **2.49a** which tautomerises to give palladium enolate **2.49b**. Coordination and migratory insertion of the alkyne creates a six-membered palladacycle **2.50** which rearomatises under base assistance to give **2.51**. A subsequent migratory insertion of a second alkyne molecule affords a strained eight-membered palladacycle **2.52**, which tautomerises to six-membered intermediate **2.53**.



Finally, reductive elimination delivers the spirocyclic product **2.48** and Pd(0) which undergoes subsequent re-oxidation to finish the catalytic cycle.

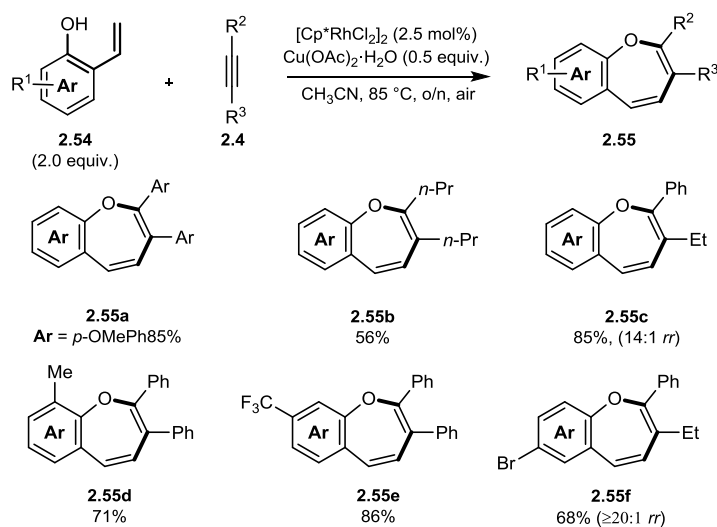


Scheme 2.27: Synthesis of spirocycles *via* Pd-catalysed double alkyne additions to 2-naphthols.^[44]

2.3.5 2-ALKENYLPHENOLS

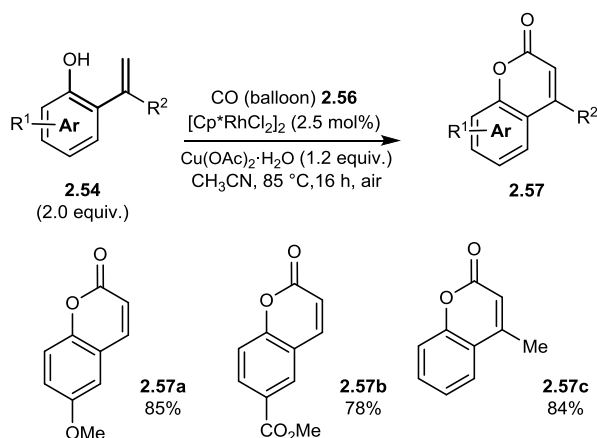
During the course of our studies regarding phenols as potential starting materials for C–H functionalisation processes (See the Research and Discussion Part), the group of Gulias and Mascareñas published similar results to those obtained in our laboratory. They investigated a [5+2] cycloaddition reaction between *o*-vinylphenols **2.54** and alkynes **2.4** under Rh catalysis (Scheme 2.28).^[45] This resulted in the formation of benzoxepine products **2.55** and proceeds *via* C–H activation of the vinyl C(sp²)–H bond followed by an annulation process. The reaction was tolerated for symmetrical diaryl-substituted alkynes (**2.55a**, **2.55d**, **2.55e**), dialkyl alkynes (**2.55b**), and for unsymmetrical alkynes (**2.55c** and **2.55f**). With the latter, the regioselectivity was high and ranged from 14:1 to $\geq 20:1$, in which the aryl group was attached to the carbon tethered to the oxygen group in the major product. Introduction of electronically differentiated substituents at the aryl ring was also tolerated (**2.55d–f**)





Scheme 2.28: Rh-catalysed formation of benzoxepine **2.55** from *o*-vinylphenols **2.54**.^[45]

The utility of this method was also applied to the synthesis of coumarins **2.57**, by the replacement of alkynes with carbon monoxide **2.56** (Scheme 2.28).



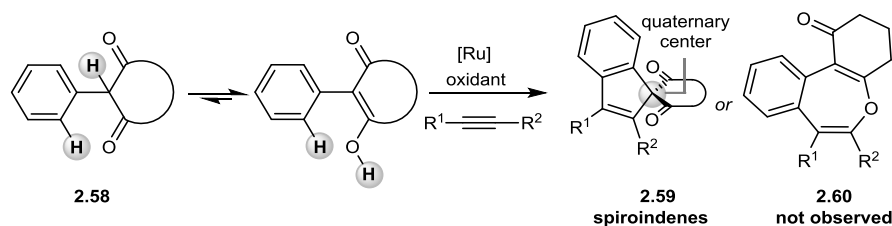
Scheme 2.29: Rh-catalysed synthesis of coumarins **2.57**.^[45]

Simultaneously, investigations carried out by our group^[46] and that of Gulias and Mascareñas,^[47] showed that 2-alkenyl phenols possessing a substituent at the internal position of the alkene, under Rh catalysis, provided the spiroenone product **2.80** rather than benzoxepine **2.55** (see the Results and Discussion Part).



2.3.6 DICARBONYLS

As discussed so far there are a wide range of *ortho*-directing groups such as carboxylic or phosphonic acids and their monoesters or benzylic alcohols which are useful for forming new C–C or C–X bonds (X = heteroatom) and thus enable alternative approaches in building a wide range of important heterocycles or carbocycles. To further broaden the library of compounds for transition-metal catalysed oxidative annulation processes, the Lam group became interested in 2-aryl-1,3-dicarbonyls. Due to the high acidity of these compounds, they exist mainly in the enol tautomeric form. This enolic intermediate possesses a hydroxyl group, similar to that presented by carboxylic acids. It was proposed that this functional group could act as a directing group for C(sp²)–H bond cleavage and react with an alkyne to form the oxidative annulated product. However, in screening this reaction the carbocyclic product **2.59** was only observed with no traces of the expected *O*-containing heterocyclic compound **2.60** (Scheme 2.30).

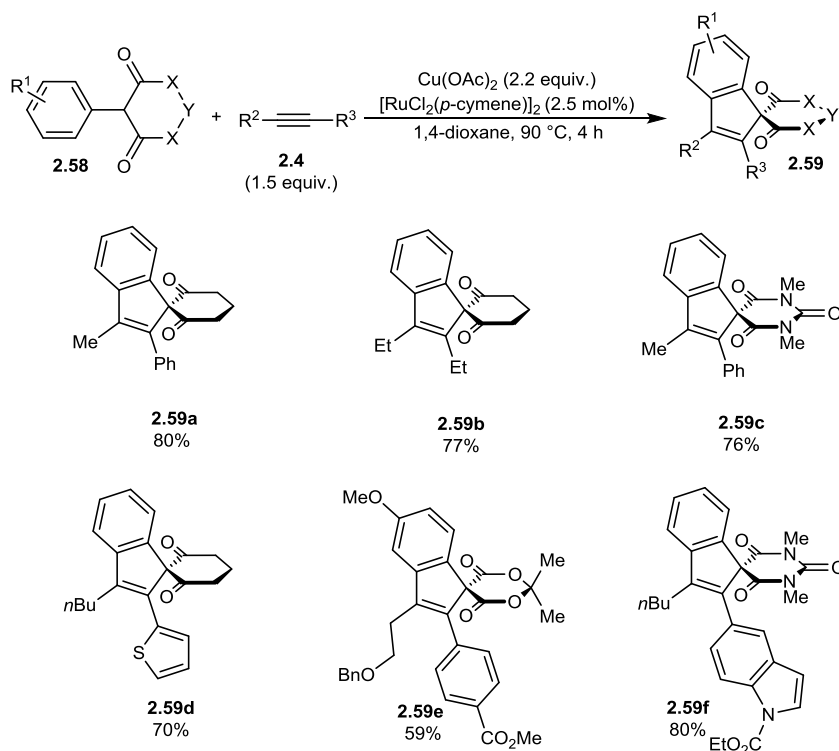


Scheme 2.30: Formation of spiroindene compounds *via* C(sp²)–H cleavage.

Pleasingly, performing the reaction of 2-aryl cyclic 1,3-dicarbonyl compounds **2.58** with alkynes **2.4** in the presence of [(RuCl₂(*p*-cymene))₂] catalyst, Cu(OAc)₂ oxidant in 1,4-dioxane at 90 °C, a range of complex spirocyclic indenenes **2.59** were achieved (Scheme 2.31).^[48] Comparable results were obtained with [Cp^{*}RhCl₂]₂ but due to the cost of the catalyst, the reaction was performed with Ru-catalyst instead. The substrate scope was not only limited to 1,3-dicyclohexanone based products **2.59a–c**, but it was also shown that the barbituric **2.59d–e** and Meldrum's acid-derived starting materials **2.59f**, underwent the annulation process successfully. However, the latter required an addition of K₂CO₃ base to push the equilibrium towards the enol tautomer, as they predominantly exist as dicarbonyls. With respect to alkynes, the



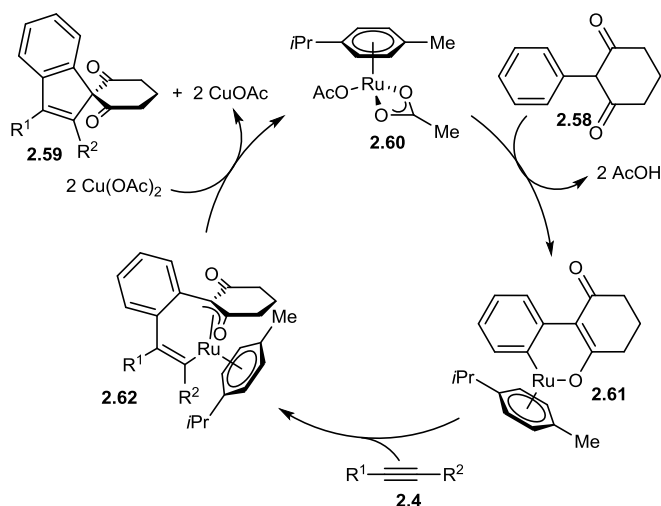
reactions proceed smoothly for symmetrical, unsymmetrical as well as for aryl/heteroaryl alkynes.



Scheme 2.31: Ru-catalysed oxidative additions of various 1,3-dicarbonyls with alkynes.^[48]

The proposed mechanism for this reaction is shown in Scheme 2.32. Under the optimised reaction conditions, the formation of an enolate occurs first, followed by the coordination with complex **2.60** to form six-membered ruthenacycle **2.61**. Coordination and migratory insertion of an alkyne **2.4**, generates a second ruthenacycle, depicted as oxa- π -allylruthenacycle **2.62**. Finally, reductive elimination of complex **2.62** gives the spiroindene product **2.59**. The oxidation of Ru(0) back to Ru(II) by $\text{Cu}(\text{OAc})_2$, re-generates the active catalyst **2.60**.



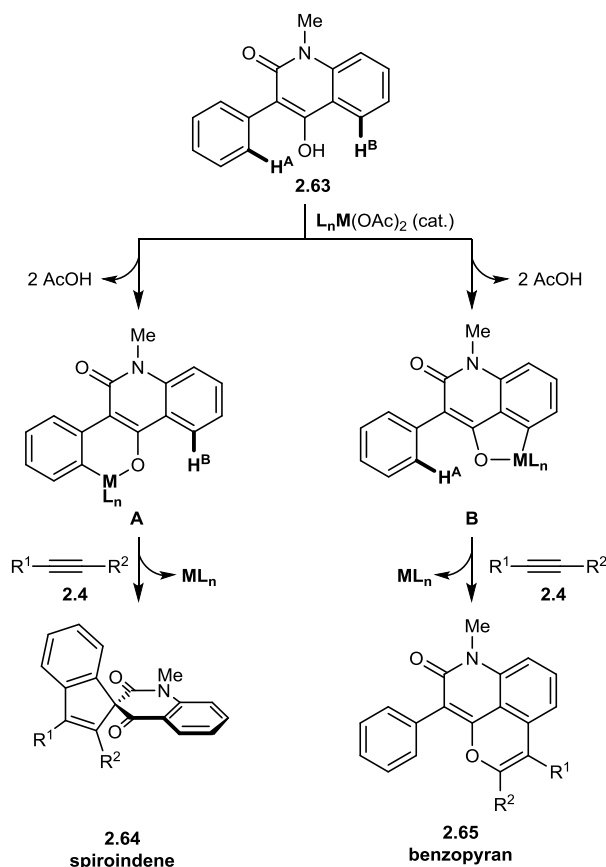


Scheme 2.32: Proposed catalytic cycle for Ru-catalysed oxidative spiroannulation.^[48]

In the previously investigated cases, the symmetrical dicarbonyl substrates only contained one possible site of reactivity for the C(sp²)-H cleavage, thus could only lead to one spiroindene product in the coupling reaction with alkynes. At this point, the Lam group wondered whether C-H functionalisation strategy could be applied for unsymmetrical substrates possessing multiple reactive C-H bonds. It was hoped that site-selectivity could be controlled by a catalyst and lead to the formation of one preferentially.

3-Aryl-4-hydroxyquinolin-2-one **2.63** was taken into this investigation as it possesses two reactive sites for enolate-directed C(sp²)-H bond cleavage, one at the 3-aryl ring **H^A** and the second one at the benzene ring of the quinolin-2-one **H^B**. If the hypothesis was right, then the site-selective and switchable C-H functionalisation with alkynes could be achieved and furnish spiroindene **2.64** or benzopyran **2.65** compounds (Scheme 2.33).^[49]

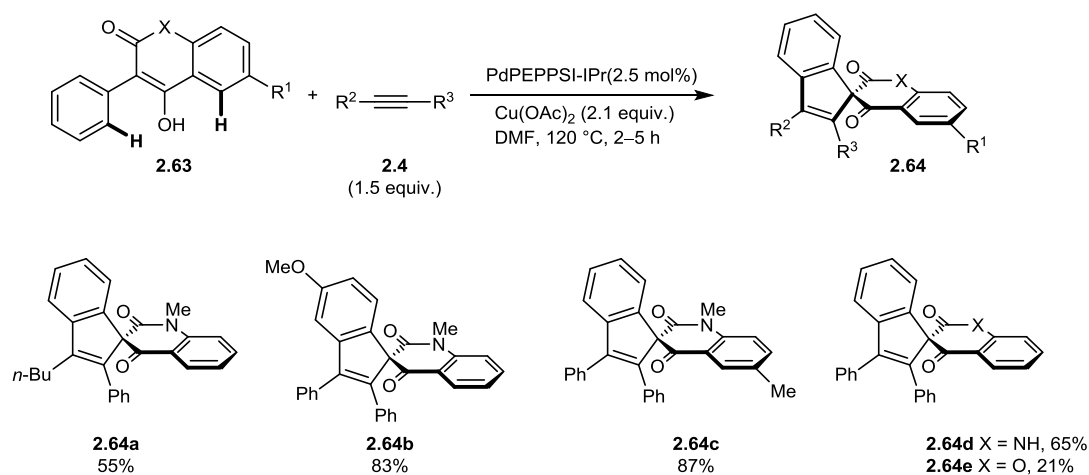




Scheme 2.33: Site-selective C–H functionalisation of 3-aryl-quinolin-2-ones with alkynes.^[49]

After intensive studies, it was found that unsymmetrical 3-aryl cyclic 1,3-dicarbonyls **2.63** did provide these two different products depending on the catalyst used in the reaction. In the presence of PdPEPPSI-IPr catalyst (2.5 mol%) and 2.1 equivalents of Cu(OAc)₂ in DMF at 120 °C, the reaction favoured the formation of spirocyclic compounds **2.64** (Scheme 2.34). In general, alkyl/aryl alkyne as well as diphenylacetylene worked fine for this transformation, giving **2.64a** and **2.64b** in 55% and 83% yield, respectively. Introduction of the methoxy substituent at the 3-aryl group (**2.64b**) or methyl at the 1,3-dicarbonyl ring (**2.64c**) was tolerated. The reaction proceeded smoothly using the free NH substrate (compound **2.64d**), however, changing for the lactone derivative was not effective and gave the final product **2.64e** in only 21% with *ca.* 90% purity.

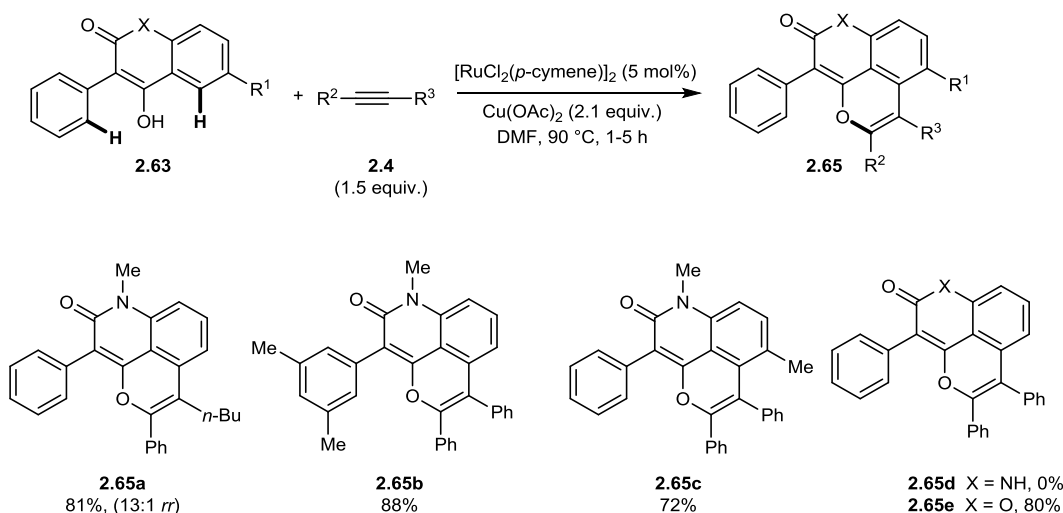




Scheme 2.34: Pd-catalysed spiroindenes formation.^[49]

An analogous experiment was conducted where unsymmetrical 3-aryl cyclic 1,3-dicarbonyls **2.63** and alkynes **2.4** were catalysed by using 5 mol% [RuCl₂(*p*-cymene)]₂ at 90 °C. This led to the formation of benzopyrans **2.65** as the major products, along with small quantities of spiroindenes **2.64** (Scheme 2.35). Similarly to the Pd-catalysed process, alkyl/aryl alkynes and diphenylacetylene were tolerated and gave the annulated products in high yields; however as a 13:1 mixture of regioisomers in case of product **2.65a**. Furthermore, substituents on the 3-aryl ring and the 1,3-dicarbonyl are tolerated, compounds **2.65b** and **2.65c**. In complete contrast to the Pd results, the free N–H starting material **2.63d** did not form any product, whereas the lactone substrate **2.63e**, which was relatively unsuccessful at forming spiroindene under the Pd-catalysis, provided benzopyran **2.65e** in 80% yield.

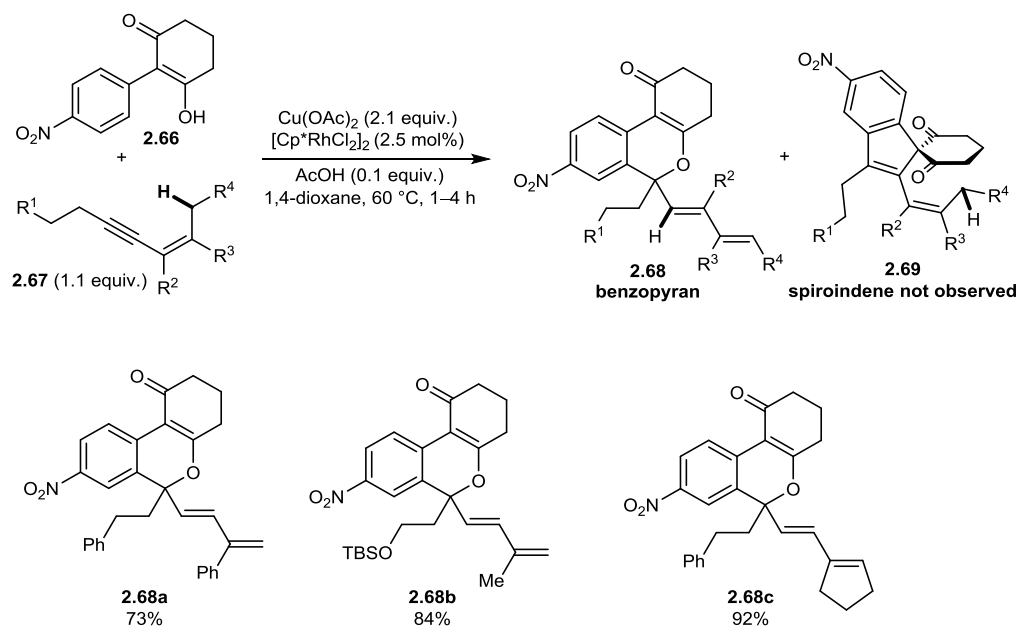




Scheme 2.35: Ru-catalysed benzopyran formation.^[49]

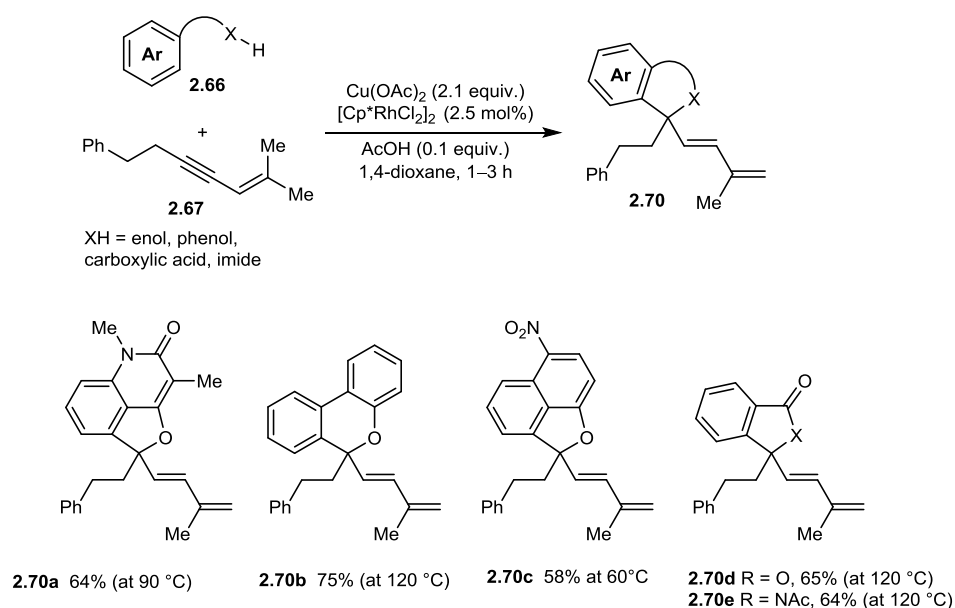
Building upon this work, the Lam group and have recently shown that electron-deficient 1,3-dicarbonyls **2.66**, in the presence of 2.5 mol% $[\text{Cp}^*\text{RhCl}_2]_2$ catalyst, 2.1 equivalents of $\text{Cu}(\text{OAc})_2$ and with the addition of 0.1 equivalent of AcOH in 1,4-dioxane at 60 °C, undergo oxidative annulation with 1,3-enynes **2.67** to give benzopyrans **2.68** (Scheme 2.36).^[50] Their studies revealed that the product formation is dependent on the electronic character of the starting material. Introduction of strongly electron-withdrawing groups at the aryl ring of the 1,3-dicarbonyls, such as nitro, led to the formation of benzopyran **2.68** as the only product. In contrast, 2-aryl-1,3-dicarbonyls possessing electron-neutral or electron-donating substituents at the aryl ring yielded the spiroindene **2.69** as the major product with some quantities of benzopyran **2.68** as a by-product (Scheme 2.36). The formation of benzopyrans was then investigated further. Under the optimised reaction conditions, a range of 1,3-enynes were screened and revealed that 1,3-enynes need hydrogen in the allylic position *cis* to the alkyne. Thus, 1,3-enynes containing a phenyl substituent *trans* to the alkyne, or a protected 2-hydroxyethyl worked well and gave the final benzopyrans **2.68a** and **2.68b** in 73% and 84% yields, respectively. This reaction was not limited to substrates containing a methylene group *cis* to the alkyne as proved by obtaining the **2.68c** product in 92% yield.





Scheme 2.36: Formation of benzopyrans from 1-aryl-1,3-dicarbonyls and 1,3-enynes.^[50]

This methodology was also applied to substrates containing other directing group such as enols, phenols, carboxylic acids, or imides to form various heterocyclic products. Selected examples are shown in Scheme 2.37.

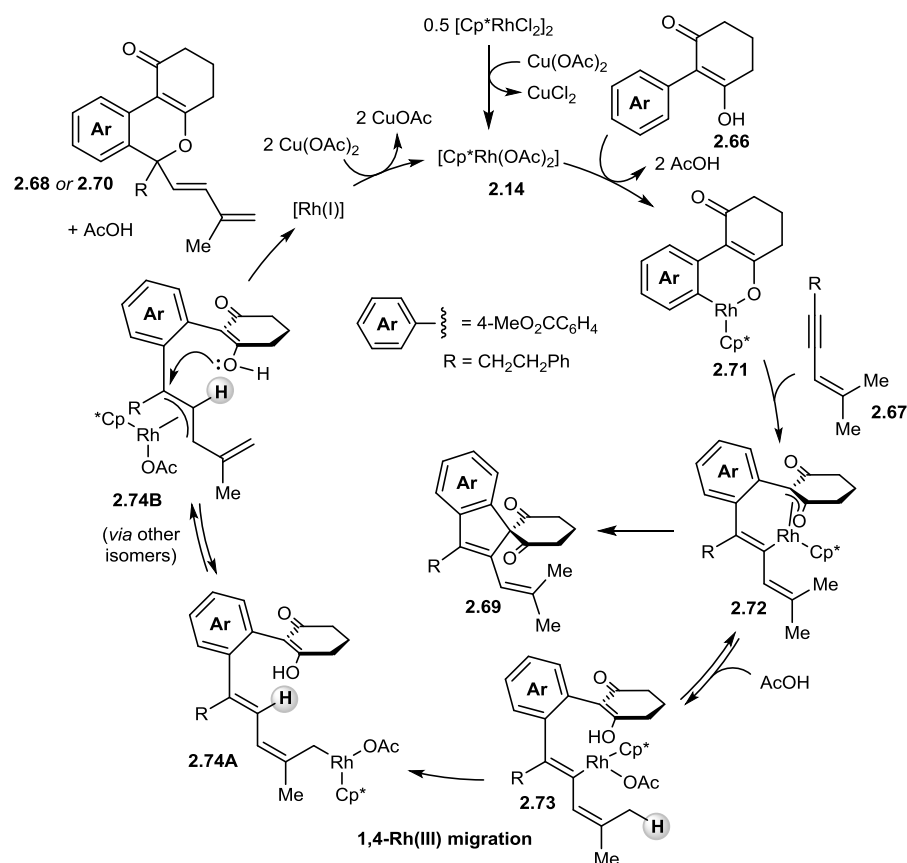


Scheme 2.37: Synthesis of heterocycles *via* 1,4-Rh migration.^[50]



The proposed catalytic cycle was evaluated and based on Fagnou's,^[51] Ackermann's,^[18] and Lam's^[49] previously reported studies regarding alkynes and 1,3-enynes in oxidative annulation reactions (Scheme 2.38). First, formation of the active catalyst **2.14** occurs *via* ligand exchange with Cu(OAc)₂. Next, C–H functionalisation of 3-aryl-1,3-dicarbonyl **2.66** forms rhodacycle **2.71**. Coordination and migratory insertion of an enyne **2.67** leads to the oxy- π -allylrhodacycle **2.72**. As described before in Scheme 2.36, formation of a spirocyclic enone **2.69** is favoured when the aryl ring of the starting material possesses electron neutral or electron-donating group, making the substrate easier to oxidise *via* reductive elimination step. However, the intermediate **2.72** may also be protonated by an addition of AcOH to form species **2.73**, which can then undergo 1,4-Rh(III) migration to give σ -allylrhodium species **2.74A**. Through isomerisation processes, formation of the π -allylrhodium species **2.74B** occurs, followed by the attack of the enolic oxygen to provide the benzopyran product **2.68** or **2.70**. Oxidation of Rh(I) with Cu(OAc)₂ regenerates the active catalyst. The key step in this reaction is 1,4-Rh(III) migration enabling an the 1,3-enyne to function as a one-carbon coupling partner. This isomerisation process can only occur when 1,3-enyne coupling partner contains an allylic hydrogen *cis* to the alkyne allowing the proposed direct 1,4-migration to happen.





Scheme 2.38: Proposed catalytic cycle of 1,4-Rh(III)-migration.^[50]

In summary, it has been highlighted that Rh, Ru and Pd-based catalysts can provide a range of complex molecules *via* oxidative annulation reactions of alkynes/1,3-enynes with various substrates possessing oxygen directing groups. The substrate scope ranges from commonly available starting materials such as carboxylic acids, benzylic alcohols, phenols or simply synthesised dicarbonyls. Based on described examples this approach is very versatile and can provide with the formation of either carbo- or heterocyclic products in a simple way.



2.4 CONCLUSION

Alkynes and 1,3-enynes are really important intermediates that have been employed in many oxidative C(sp²)-H functionalisation reactions with a variety of commercially available starting materials. The interest of this methodology is still high as the annulated carbocyclic and heterocyclic products can be achieved in a simple and sustainable way. The possibility to run these reactions under low catalyst loading and under air has been already achieved but still opens up opportunities to discover this area in depth.

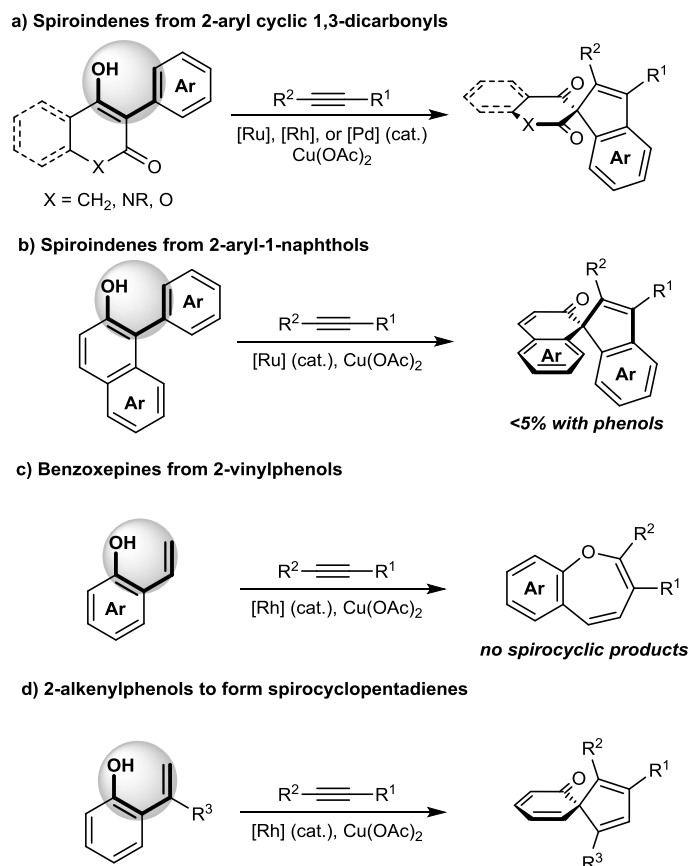


2.5 RESEARCH AND DISCUSSION

Unless stated otherwise conversion and regioselectivity ratio were determined by ^1H NMR analysis of the unpurified reaction mixtures. Yields are of pure isolated products.

As previously reported by our group, 2-aryl 1,3-dicarbonyls were effective substrates in the oxidative annulation reaction with alkynes and provided a range of interesting carbocyclic spiroindene products (Scheme 2.39a).^{[48],[49]} The efficiency of the reaction was due to the enol moiety embedded within the 1,3-dicarbonyl, as it acted as a directing group for the $\text{C}(\text{sp}^2)\text{--H}$ bond functionalisation. At this stage, we wondered if 2-alkenylphenols, possessing a similar hydroxyl group, could serve as good coupling partners (Scheme 2.39d). During the course of our studies, the group of Luan and co-workers showed that 1-aryl-2-naphthols can undergo a dearomatising oxidative annulation reaction with alkynes under Ru-catalysis;^[43] however, the reaction conditions were not effective for phenol-derived substrates (Scheme 2.39b). Moreover, work from Gulias and Mascareñas employing 2-vinylphenols as directing groups in C–H functionalisation reactions provided the benzoxepine product, rather than the spirocyclic enone (Scheme 2.39c).^[45] Having assessed the work of our group and others, we focused towards finding suitable conditions that would allow the formation of spiroannulated carbocycles from the dearomatising oxidative annulation of 2-alkenylphenols.





Scheme 2.39: Enol-directed oxidative annulation of related substrates with alkynes.^[46]

2.5.1 SYNTHESIS OF VARIOUS SUBSTITUTED 2-ALKENYLPHENOLS

Our investigation started with the synthesis of a range of various 2-alkenylphenols **2.79**. In general, most of these were obtained from a lithiation reaction of 2-(2-bromophenoxy)-tetrahydro-2*H*-pyran **2.75** using *n*-BuLi to give aryl lithium **2.76**. Addition of the appropriate ketone **2.77** then gave tertiary alcohols **2.78** which on dehydration using concentrated H₂SO₄ gave access to a range of 2-alkenylphenols **2.79** (Table 1.1).



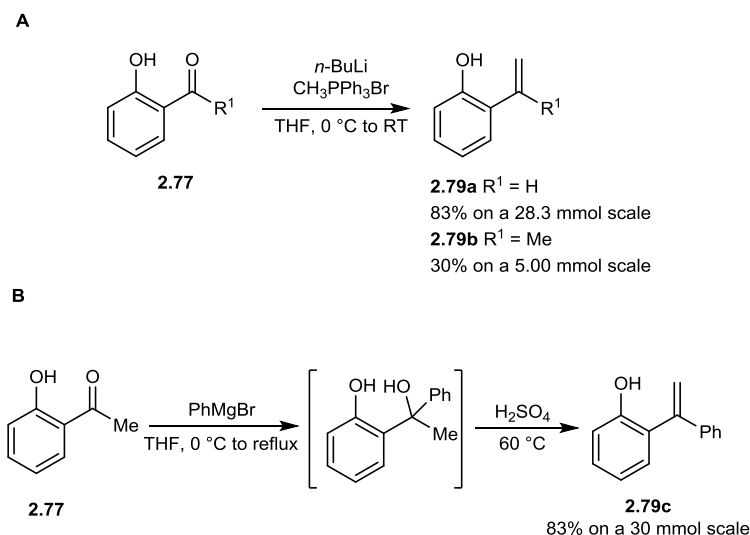
Table 1.1 Synthesis of various 2-alkenylphenols.

Entry	Product		Yield (%)
1 ^a		2.79d	52 ^[46]
2 ^a		2.79e	49 ^[46]
3 ^a		2.79f	50 ^[46]
4 ^c		2.79g	58 ^[46]
5 ^a		2.79h	56 ^[52]
6 ^a		2.79i	53 ^[46]
7 ^b		2.79j	49 ^[46]
8 ^a		2.79k	70 ^[53]
9 ^c		2.79l	38 ^[53]
10 ^b		2.79m	37 ^[46]
11 ^b		2.79n	35 ^[46]

Reactions conducted on a: ^a2 mmol, ^b3 mmol, ^c4 mmol scale



The Wittig reaction was employed for the synthesis of **2.79a**^[54] and **2.79b** giving 83% and 30% yield, respectively (Scheme 2.40A). 2-Phenylvinyl phenol **2.79c** was obtained by addition of Grignard reagent PhMgBr to 2'-hydroxyacetophenone **2.77** followed by acid-catalysed dehydration (Scheme 2.40B).



Scheme 2.40: Synthesis of various starting materials.

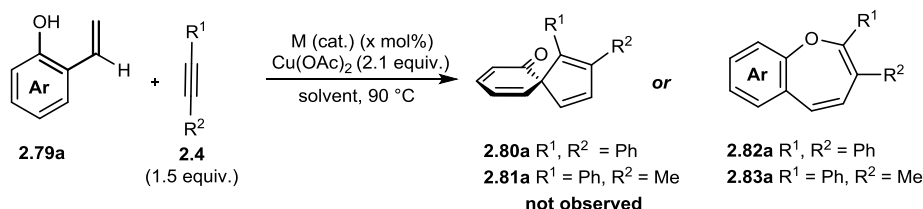
2.5.2 CATALYTIC SYSTEM

After the synthesis of starting materials, we focused on their application as potential coupling partners in oxidative annulation reactions with alkynes. Thus, the screening of potential catalyst systems began. As a model reaction we chose 2-vinylphenol **2.79a** and commercially available alkynes: diphenylacetylene **2.4a** and 1-phenyl-1-propyne **2.4b**. Initial catalyst screening showed that the combination of [Cp^{*}RhCl₂]₂ catalyst and Cu(OAc)₂ as an oxidant was a good choice. (Table 1.2, entries 1–2). However, the expected spirocyclic enone products **2.80a** and **2.81a** were not obtained. The NMR spectroscopic analysis showed the formation of benoxepine products **2.82a** and **2.83a** instead, in 67% and 74% yield, respectively. Similar results were reported by Gulias and Mascareñas during the course of our research.^[45] Further investigation of commonly used catalysts for oxidative annulation of alkynes such as [RuCl₂(*p*-cymene)]₂ and Pd(II) catalysts such as Pd(OAc)₂, Pd₂(dba)₃, PEPPSI-IPr were not effective for this transformation, giving the final product in less



than 10% conversions (entries 3 and 4), as a complex mixture of products (entry 5) or no product formation at all (entries 8 and 9).

Table 1.2: Initial catalysts screening.



Entry	R ¹	R ²	Catalyst	Solvent	Conversion (yield) of 2.82a or 2.83a (%)
1	Me	Me	[Cp*RhCl ₂] ₂	DMF	67 yield ^a
2	Ph	Ph	[Cp*RhCl ₂] ₂	DMF	74 yield ^a
3	Me	Me	[RuCl ₂ (<i>p</i> -cymene)] ₂	DMF	<10 ^b
4	Ph	Ph	[RuCl ₂ (<i>p</i> -cymene)] ₂	DMF	<10 ^b
5	Ph	Ph	[RuCl ₂ (<i>p</i> -cymene)] ₂	<i>t</i> -AmOH	<5 ^c
6	Ph	Ph	PEPPSI-IPr	DMF	<5 ^{b,f}
7	Ph	Ph	Pd(OAc) ₂	DMF	Complex Mixture ^{d,f}
8	Ph	Ph	[Pd ₂ (dba) ₃]/ 1,10-phenanthroline	1,4-dioxane	<5 ^e
9	Me	Me	[Pd ₂ (dba) ₃], 1,10-phenanthroline	1,4-dioxane	<5 ^e

Reaction conditions: ^aRh(III) (2.5 mol%); ^b[M] (5 mol%); ^cRu(II) (2.5 mol%), K₂CO₃ (0.20 mmol); ^dPd(II) (5.0 mol%); ^ePd(II) (10 mol%), 1,10-phenanthroline (20 mol%), NaOAc (5 equiv.); ^fReaction conducted at 120 °C

Next, the reaction of vinylphenol **2.79a** and diphenylacetylene **2.4a** catalysed by [Cp*RhCl₂]₂ was run in various solvents and at different temperatures: in toluene at 60 °C, DCE at 90 °C and *t*-Am-OH at 90 °C. None of these reactions went to completion after stirring for 20 h. Lowering Cu(OAc)₂ loading from 2.1 equivalents to 50 and 20 mol% in DMF at 50 °C revealed a drop in conversion from 99% to 75% and 64 %, respectively.

The choice of substrate proved a major turning point in this project. When phenylvinyl phenol **2.79c** and diphenylacetylene **2.4a** were introduced into the optimised reaction conditions (Table 1.3, entry 1), it was noted that the final product

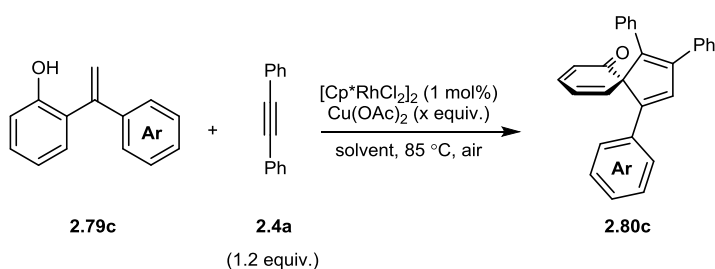


was the dearomatised spirocyclic enone **2.80c**. As the yield of the reaction was only 50%, our efforts were directed towards the optimisation of this process.

As demonstrated by the group of Gulias and Mascareñas,^[45] running the reactions of 2-vinylphenols in acetonitrile was necessary for the synthesis of benzoxepine products in high yield. These reaction conditions were next investigated for the formation of spirocyclic enone **2.80c**. Gratifyingly, an improvement in yield was also noticed and reached 74% in comparison to the reaction run in DMF (Table 1.3, entry 2). Due to the fact that rhodium metal abundance is low and the price of the catalyst is high, our efforts focused on lowering the catalyst loading and whilst retaining the high yield. Surprisingly, the reactivity of the reaction was the same and the final product **2.80c** was obtained in 83% yield using just only 1 mol% of rhodium catalyst (Table 1.3, entry 3). We then examined the oxidant loading. It is possible to limit the stoichiometric by-products to water by running the reaction under catalytic amount of Cu(OAc)₂ (5 mol%), [Cp*RhCl₂]₂ (1 mol%) and balloon of air (Table 1.3, entry 6). Varying the loading of Cu(OAc)₂ from sub- to super-stoichiometric, showed no big change in terms of the reaction yield (Table 1.3, entries 2–5).



Table 1.3: Optimisation of spirocyclic enone product.



Entry	$\text{Cu}(\text{OAc})_2$ (equiv.)	Solvent	Temperature (°C)	Yield (%)
1	2.1	DMF	50	50
2	2.1	CH_3CN	85	74 ^a
3	0.5	CH_3CN	85	83
4	0.2	CH_3CN	85	77
5	0.1	CH_3CN	85	77
6	0.05	CH_3CN	85	83

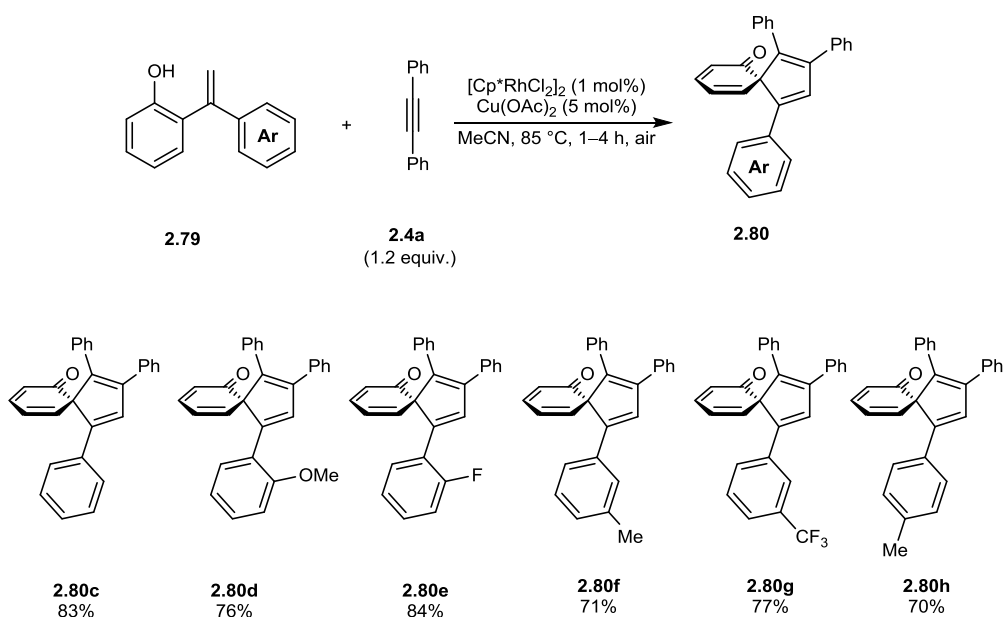
^aReaction conducted with 2.5 mol% of $[\text{Cp}^*\text{RhCl}_2]_2$

2.5.3 SUBSTRATE SCOPE:

- Alkynes**

Next, the optimised conditions were applied to a range of 2-alkenylphenols **2.79c–h** to provide access to various dearomatised spirocyclic compounds **2.80c–h** (Scheme 2.41). Gratifyingly, introduction of the substituents at the *ortho*-position of the non-phenolic aromatic ring worked well, regardless of the electronic character of the substituent, and gave the final products **2.80d** and **2.80e** in high yields, 76% and 84%, respectively. Similarly, incorporation of the substituents at the *meta*- or *para*-position did not affect the yields of the reactions (compounds **2.80f–2.80h**).





Scheme 2.41: Synthesis of various spirocyclic enones with diphenylacetylene.

When unsymmetrical alkyl/aryl-substituted-alkyne, 1-phenyl-1-propyne **2.4b**, was tested in place of diphenylacetylene **2.4a** under optimised reaction conditions, the expected spirotetraenone **2.81** was obtained in only moderate yield. Even the introduction of a slightly higher catalyst loading $[\text{Cp}^*\text{RhCl}_2]_2$ (2.5 mol%) and $\text{Cu}(\text{OAc})_2$ (20 mol%) succeeded in 51% yield (Figure 2.1, compound **2.81a**). As the reactivity of alkyl aryl alkynes in comparison to diaryl alkynes is significantly lower in this oxidative spiroannulation process, a longer reaction time is needed for the substrate consumption. However, at the same time decomposition of the product was observed due to the product's thermal instability. This problem was overcome by using super-stoichiometric $\text{Cu}(\text{OAc})_2$ (2.1 equivalents) at a lower temperature of 65 °C (Scheme 1.3, compounds **2.81a** and **2.81b**). Furthermore, in all cases, only a single regioisomer was detected by NMR analysis of the crude reaction mixture. The X-ray analysis of the purified product also confirmed the structure. It is believed that in case of unsymmetrical alkynes the formation of spirocyclic enone as the only one regioisomer is due to the polarisation of the triple bond in alkyne by the aromatic substituent. The development of small, positive charge facilitates the C–C bond formation. As a result of that, rhodium is then attached to the carbon next to the aromatic ring (Scheme 2.46).



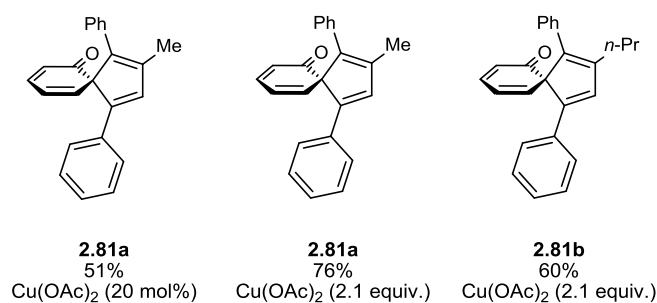


Figure 2.1: Reactions of 2-(1-phenylvinyl)phenol with unsymmetrical alkynes.

Finally, to further demonstrate the utility of our method, we applied our conditions to more challenging substrates: terminal **2.82a**, dialkyl **2.82b**, and protected alkynes **2.82c** and **2.82d**. Unfortunately, a complex mixture of products was obtained in all cases, regardless of the reaction conditions employed (Figure 2.2).

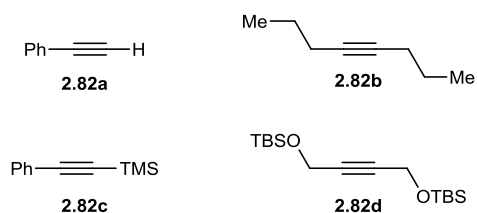
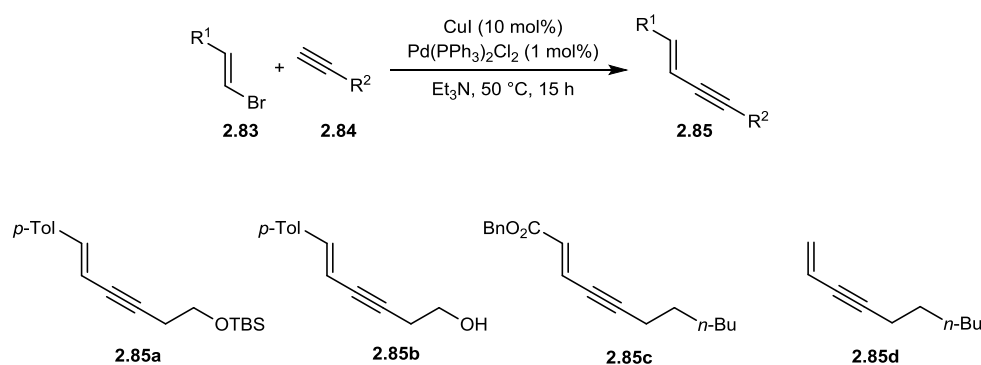


Figure 2.2: Screening of terminal, dialkyl and protected alkynes.

- **1,3-Enynes**

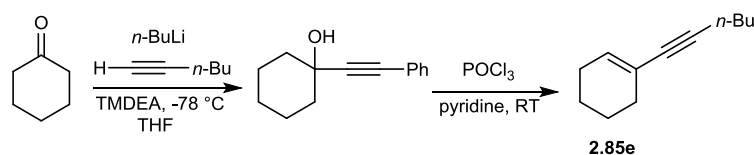
Having assessed the scope of alkynes tolerated for the oxidative spiroannulation process, our attention was focused next towards different coupling partners to further expand the scope of the reaction. In this context, 1,3-enynes were then examined. A number of these substrates were synthesised during a previous project within our laboratory by Dr David Burns and Martin Wieczysty. In general, they were obtained in a Sonogashira coupling between an arylalkenyl halide and terminal alkyne. However, some alkenyl bromides are not commercially available and it was required to synthesise these according to literature procedures.^{[55],[56]}





Scheme 2.42: Synthesis of 1,3-enynes using Sonogashira coupling procedures

Alternatively, 1,3-enyne 1-(hex-1-ynyl)cyclohexyl-1-ene **2.85e** was obtained using the following method of Yoshida a two-step synthesis process, starting from cyclohexanone (Scheme 2.43).^{[57],[51]}

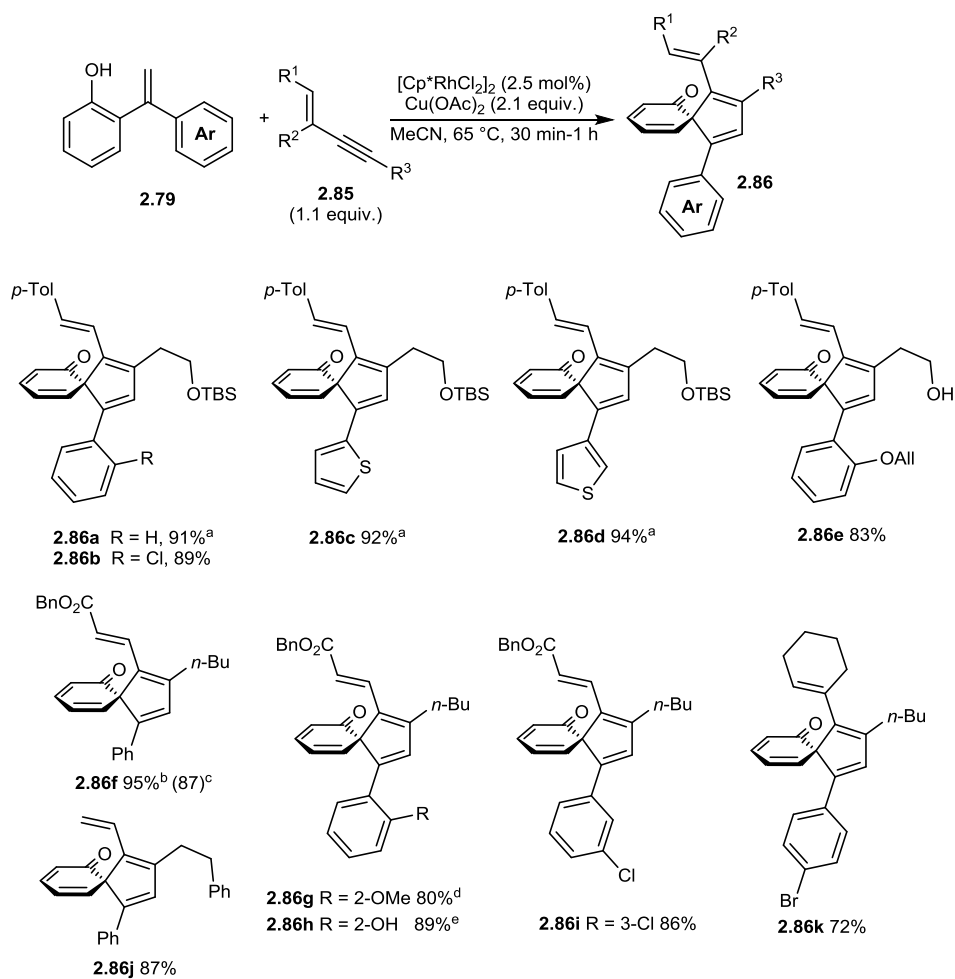


Scheme 2.43: Synthesis of 1,3-enyne **2.85e**.

1,3-Enynes were next examined under the optimised conditions for the oxidative annulation process. Pleasingly, all of the tested substrates provided the final spirocyclic enones **2.86a–k** in high yields as a single regioisomer in the presence of super-stoichiometric $\text{Cu}(\text{OAc})_2$ at 65 °C (Scheme 2.44). It was observed that various substituents in the alkene component of the 1,3-enyne were tolerated. Compounds **2.86a–e** with *p*-methylstyryl, benzoate **2.86f–i**, vinyl **2.86j**, cyclohexenyl **2.86k** groups all gave excellent yields with a range of electronically diverse 2-[1-(hetero)arylvinyl]phenols **2.79**. Furthermore, incorporation of a simple alkyl **2.86f–k**, and oxygenated alkyl substituents **2.86a–c** on the alkyne part of the 1,3-enyne was also tolerated as was an unprotected alcohol **2.86e**. We also successfully screened 2-(1-arylalkenyl)phenols which contained various substituents at the non-phenolic ring at the *ortho*-position: 2-chloro **2.86b**, 2-allyloxyl **2.86e**, 2-methoxy **2.86g**, 2-hydroxy **2.86h**, *meta*-position: 3-chloro **2.86i** and *para*-position: 4-bromo **2.86k**. Gratifyingly,



we also discovered that thienyl-containing substrates (**2.86c** and **2.86d**) were also effective in providing good results, despite the possibility of poisoning the catalyst by sulfur coordination to the metal centre. All of the described reactions proceeded with >19:1 regioselectivity. The use of a catalytic amount of Cu(OAc)₂ (5 mol%) under air was also investigated in this spiroannulation process with 1,3-enynes. The formation of a final product in lower 87% yield was observed in comparison to 97%, when superstoichiometric amount of Cu(OAc)₂ was used **2.86f**.



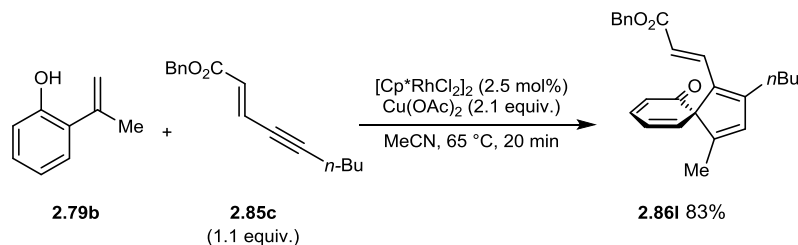
Scheme 2.44: Synthesis of spirocyclic enones with various enynes.

^aReaction time was 15 min; ^bReaction time was 30 min.

^cReaction conducted with Cu(OAc)₂ (5 mol%) under air at 85 °C for 5 h; ^dUsing 1.2 equiv. of enyne, ^eReaction conducted at 40 °C for 2 h.



In addition, we have also shown that this methodology is not only limited for substrates containing a (hetero)aryl substituent at the 1-position of an alkene but the reaction of 2-alkenylphenol **2.79b** with 1,3-enyne **2.85c** also gave the dearomatised product **2.86l** in 83% yield as shown in Scheme 2.45 below.

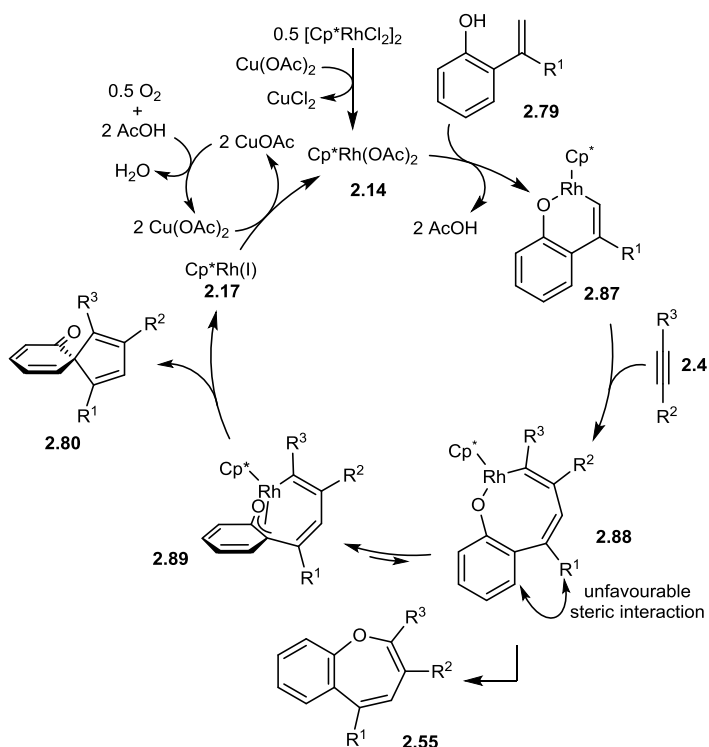


Scheme 2.45: Synthesis of spirocyclic enone **2.86l** from 2-alkenylphenol **2.79b**.

2.5.4 POSTULATED CATALYTIC CYCLE

The postulated mechanism of the dearomatising oxidative spiroannulation of alkynes and 1,3-enynes with 2-alkenylphenols is shown below in Scheme 2.46 and follows the described mechanism for similar processes in the literature.^[45] First, the formation of an active catalyst rhodium(III) diacetate **2.14** occurs by ligand exchange with $\text{Cu}(\text{OAc})_2$, followed by the phenol-directed functionalisation of substrate **2.79** to give the six-membered rhodacycle **2.87**. Then, coordination and migratory insertion of an alkyne generates the rhodacycle **2.88**. When $\text{R}^1 = \text{H}$, then a new C–O bond formation occurs *via* reductive elimination giving benzoxepine product **2.55**. This postulated pathway has been reported previously by Gulias and Mascareñas.^[45] However, in our studies, when R^1 is not hydrogen, we believe that isomerisation of **2.88** into rhodacycle **2.89** occurs because of steric interactions between R^1 and the phenoxide ring. The final spiroenone product **2.80** is formed *via* C–C reductive elimination step releasing Rh(I) **2.17** catalyst which undergoes oxidation with $\text{Cu}(\text{OAc})_2$ to regenerate the active catalyst species.

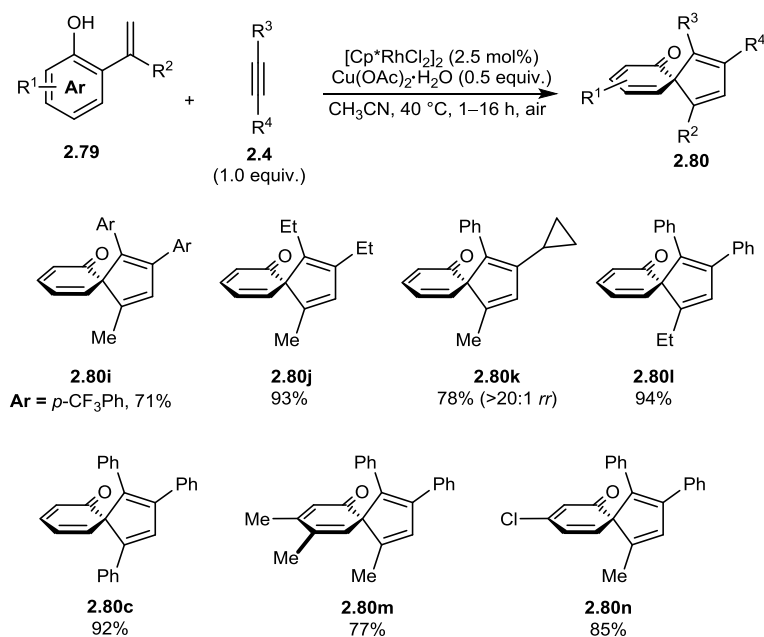




Scheme 2.46: Proposed catalytic cycle.^{[46],[47]}

Simultaneously, Gulias and Mascareñas published similar work in regards to alkyne oxidative annulation reactions with 2-alkenylphenols under rhodium catalysis. The scope revealed that symmetrical alkyl and aryl alkynes were tolerated in this reaction. In terms of unsymmetrical alkynes, only one regioisomer was observed by NMR spectroscopy and its structure was confirmed by X-ray analysis. The placement of a substituent at the internal position of an alkene, such as methyl, ethyl or phenyl was successful for the reaction outcome (**2.80c**, **2.80i–n**). Changing the electronic character of a phenol ring, by introducing various functional groups, e.g. dimethyl or chloro, led to the formation of **2.80m** and **2.80n** in 77% and 85% yield, respectively.





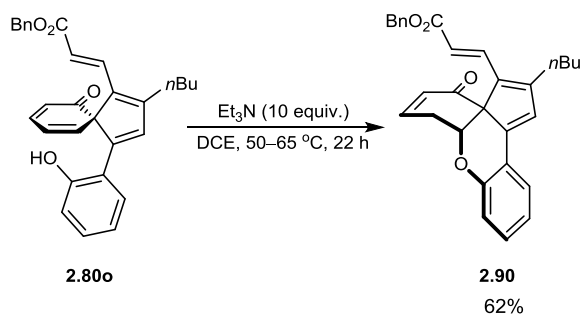
Scheme 2.47: Synthesis of spirocyclic enones under Rh-catalysed oxidative annulation of 2-alkenyl phenols **2.79** by Gulias and Mascareñas.^[47]

The mechanism of the reaction is in accordance with the one proposed by our group.^{[46],[47]}



2.5.5 PRODUCT UTILITY

To demonstrate the utility of the oxidative spiroannulation methodology, manipulation of a spiroproduct was investigated. By treating product **2.80o**, that contains an electrophilic dienone and a nucleophilic phenol, with Et_3N resulted in the formation of the highly functionalised tetracycle **2.90**. This 1,6-addition proceeds *via* the attack of the phenoxide onto the dienone. We also recovered 18% of the unreacted starting material (Scheme 2.48).

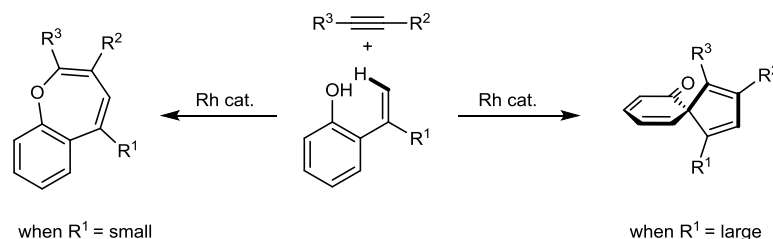


Scheme 2.48: Formation of tetracycle **2.90** via 1,6-addition.



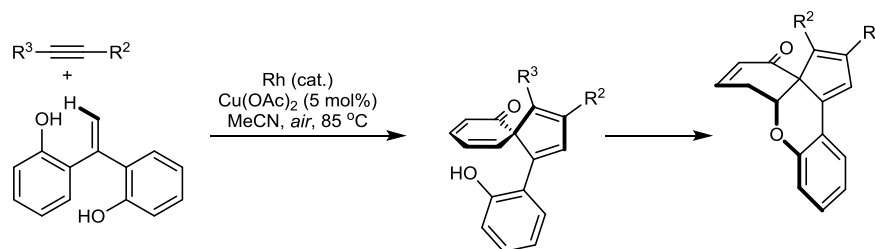
2.6 CONCLUSIONS AND FUTURE WORK

We have developed the synthesis of highly complex spirocyclopentadienes in high yields *via* the oxidative annulation reaction between 2-alkenyl phenols and alkynes utilising a rhodium catalyst. The nature of the substitution on the alkenyl phenol was found to be incredibly important, small substituents led to the formation of a seven-membered heterocyclic product, while bulkier groups in this position led to the intriguing spirocyclic product.



Scheme 2.49: The divergent reactions of 2-alkenylphenols under rhodium catalysis.

The resultant 1,6-enones could also be exploited by using a starting material that featured a nucleophilic moiety which could then undergo conjugate addition to give high functionalised tetracyclic products.



Scheme 2.50: The formation for tetracyclic products.

Recently numerous groups have developed enantioselective C–H functionalisation protocols^[5] and given that the spirocyclic products feature a stereocentre, we intend to investigate whether similar catalytic systems can be successfully applied to our methodology to generate the same products in a stereoselective manner. Similarly our group have exploited 1,3 enynes that feature *cis* allylic protons as both one-carbon annulation partners and three-carbon annulation partners^[50] *via* a 1,4 Rh-migration pathway and it may be possible to use this methodology along with alkenylphenols to generate complex cyclic systems.



2.7 EXPERIMENTAL PART

This project was done in the collaboration with two of my work colleagues Dr Daniel Best and Dr David Burns. The data presented in this section represents experiments performed by me in regards to this project.

General information

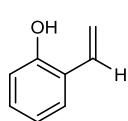
Unless specified otherwise, all reactions were carried out under an atmosphere of nitrogen using oven-dried glassware. Et₂O and THF were dried and purified by passage through activated alumina columns using a solvent purification system. Unless specified otherwise, all other commercially available reagents and solvents were used as received. All petroleum ether used was 40–60 °C petroleum ether. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F₂₅₄ 0.2 mm precoated plates. Compounds were visualised by exposure to UV light or by dipping the plates into solutions of potassium permanganate or vanillin followed by heating. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35–70 micron). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The solvent of recrystallisation is reported in parentheses. Infra-red spectra were recorded on a Nicolet Avatar 360 FT instrument on the neat compound using an attenuated total reflection (ATR) accessory with a diamond crystal and a germanium sample plate. NMR spectra were acquired on either a Bruker AV(III)500, Bruker AV400, AV(III)400, DPX400 or a DPX300 spectrometer. ¹H and ¹³C NMR spectra were referenced to external tetramethylsilane *via* the residual protonated solvent (¹H) or the solvent itself (¹³C). All chemical shifts are reported in parts per million (ppm). For CDCl₃, the shifts are referenced to 7.27 ppm for ¹H NMR spectroscopy and 77.0 ppm for ¹³C NMR spectroscopy. For (CD₃)₂CO, the shifts are referenced to 2.05 ppm for ¹H NMR spectroscopy and 29.84 ppm for ¹³C NMR spectroscopy. All ¹⁹F NMR spectra were proton-decoupled. High-resolution mass spectra were recorded using electrospray ionisation (ESI) techniques at the School of Chemistry, University of Edinburgh, or at the School of Chemistry, University of Nottingham.



Substrate synthesis:

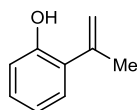
General Procedure A: Synthesis of compounds **2.79a** and **2.79b** using a modification of Manabe's procedure^[54]

To a solution of methyltriphenylphosphonium bromide in THF at 0 °C was added *n*-BuLi and the mixture was warmed to room temperature and then stirred at reflux for 1 h. The reaction mixture was cooled to 0 °C and the corresponding aldehyde or ketone was added. The vessel was allowed to warm to room temperature and stirred for 2.5 or 6 h. The reaction was then diluted with Et₂O, washed with 1:1 brine/sat. NH₄Cl and brine, dried over MgSO₄ and concentrated *in vacuo*.



2-ethenylphenol (2.79a)^[54]

The title compound was prepared according to the General Procedure A using methyltriphenylphosphonium bromide (10.11 g, 28.30 mmol), *n*-BuLi (2.5 M in hexanes, 11.5 mL, 28.3 mmol) and salicylaldehyde (1.30 mL, 12.3 mmol) for a reaction time of 2.5 h and was purified by flash chromatography (0 to 20% EtOAc/hexane) to give **2.79a** (1.32 g, 89%) as a colourless oil. Physical and spectral properties were in accordance with those reported in the literature.^[54]



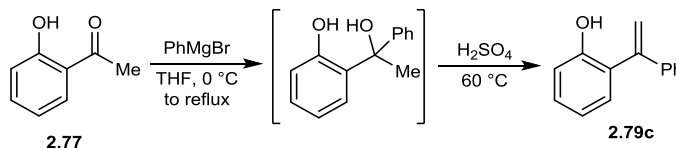
2-(Prop-1-en-2-yl)phenol (2.79b)^[54]

The title compound was prepared according to the General Procedure A using methyltriphenylphosphonium bromide (3.93 g, 11.0 mmol), *n*-BuLi (1.6 M in hexanes, 6.9 mL, 11 mmol) and 2'-hydroxyacetophenone (0.60 mL, 5.0 mmol) for a reaction time of 6 h and was purified by flash chromatography (0 to 10% EtOAc/petroleum ether) to give **2.79b** (201 mg, 30%) as a colourless oil. Physical and spectral properties were in accordance with those reported in the literature.^[54]



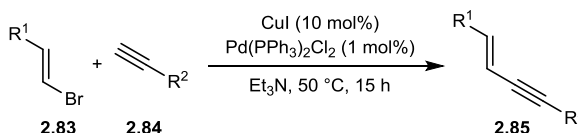
General Procedure B: Preparation of **2.79c**

2-(1-Phenylvinyl)phenol (**2.79c**)^[52]



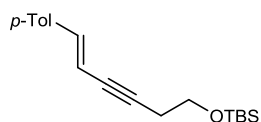
To a solution of 2'-hydroxyacetophenone **2.77** (3.6 mL, 30 mmol) in dry THF (50 mL) at 0 °C was added phenylmagnesium bromide (3.0 M in Et_2O , 20 mL, 60 mmol). The mixture was stirred at reflux for 24 h, cooled to 0 °C and conc. H_2SO_4 (2.0 mL, 38 mmol) was added over *ca.* 1 min with vigorous stirring. The mixture was stirred at 60 °C for 16 h, cooled to room temperature, diluted with Et_2O (100 mL), washed with 1:1 brine/sat. NaHCO_3 (2×100 mL) and brine (50 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification of the residue by flash column chromatography (4 to 40% CH_2Cl_2 /petroleum ether) gave **2.79c** (4.78 g, 81%) as a yellow oil. Physical and spectral properties were in accordance with those reported in the literature.^[52]

General Procedure C: Preparation of Enynes



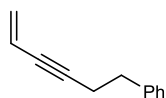
To a solution of the appropriate alkenyl bromide (1 equiv.), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (1 mol%) and CuI (10 mol%) in Et_3N was added the appropriate alkyne (1.1 equiv) and the mixture was stirred at 50 °C for 15 h. The reaction mixture was cooled to room temperature, diluted with Et_2O (50 mL), washed with brine (50 mL), and the aqueous layer was further extracted with Et_2O (2×50 mL). The organic layers were combined, dried with MgSO_4 and concentrated *in vacuo*. Purification of the residue by flash column chromatography (2% EtOAc /petroleum ether) gave the enyne **2.85**





***tert*-Butyldimethyl-[(*E*)-6-(4-methylphenyl)hex-5-en-3-yn-1-yl]oxy silane (**2.85a**)**

The title compound was prepared according to General Procedure C using (*E*)-1-(2-bromovinyl)-4-methylbenzene^[56] (985 mg, 5.00 mmol), Pd(PPh₃)₂Cl₂ (35 mg, 50 μmol) and CuI (95 mg, 0.50 mmol), and 4-(*tert*-butyldimethylsilyloxy)-1-butyne (1.01 g, 5.50 mmol) to give enyne **2.58a** (1.24 g, 82%) as an orange oil. *R*_f 0.74 (10% EtOAc/petroleum ether); IR 2953, 2928, 2857, 1514, 1462, 1252, 1101, 1055, 835, 775 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.27 (2H, d, *J* = 8.0 Hz, 2 × ArH), 7.13 (2H, d, *J* = 8.0 Hz, 2 × ArH), 6.87 (1H, d, *J* = 16.2 Hz, ArCH=CH), 6.10 (1H, dt, *J* = 16.2, 2.2 Hz, ArCH=CH), 3.80 (2H, t, *J* = 7.2 Hz, CH₂O), 2.60 (2H, td, *J* = 7.2, 2.2 Hz, CH₂CH₂O), 2.35 (3H, s, ArCH₃), 0.93 (9H, s, C(CH₃)₃), 0.11 (6H, s, 2 × SiCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 140.4 (CH), 138.3 (C), 133.7 (C), 129.3 (2 × CH), 126.0 (2 × CH), 107.5 (CH), 89.1 (C), 80.9 (C), 62.0 (CH₂), 25.9 (3 × CH₃), 24.0 (CH₂), 21.3 (CH₃), 18.4 (C), -5.26 (CH₃), -5.33 (CH₃); HRMS (ESI +ve) Exact mass calculated for C₁₉H₂₈O₂₃NaSi [M+Na]⁺: 323.1802, found: 323.1801.

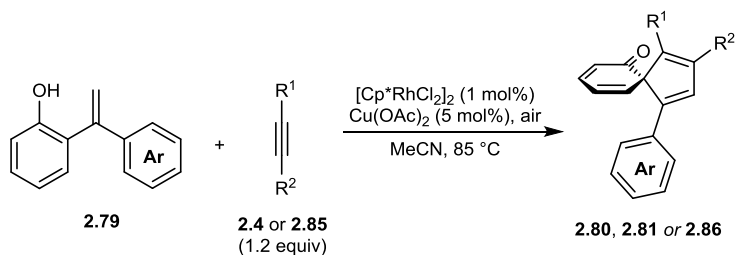


Hex-5-en-3-yn-1-ylbenzene (2.85d**)**

The title compound was prepared according to a modification of General Procedure C (in that the vinyl bromide was used in excess (1.5 equiv.) and the chromatography eluent was petroleum ether) using vinyl bromide (1.0 M in hexanes, 11.5 mL, 11.5 mmol) and 4-phenyl-1-butyne (1.00 g, 7.70 mmol) to give enyne **2.85d** (664 mg, 55%) as a yellow oil. *R*_f 0.50 (petroleum ether); IR 3028, 2927, 1604, 1469, 1453, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.28 (2H, m, ArH), 7.26–7.20 (3H, m, ArH), 5.79 (1H, ddt, *J* = 17.5, 11.0, 2.2 Hz, CH₂=CH), 5.56 (1H, ddd, *J* = 17.5, 2.2, 0.5 Hz, CH_AH_B=), 5.40 (1H, dd, *J* = 11.0, 2.2 Hz, CH_AH_B=), 2.87 (2H, t, *J* = 7.4 Hz, CH₂Ph), 2.60 (2H, td, *J* = 7.0, 2.2 Hz, CH₂CH₂Ph); ¹³C NMR (100.6 MHz, CDCl₃) δ 140.6 (C), 128.42 (2 × CH), 128.36 (2 × CH), 126.3 (CH), 125.8 (CH₂), 117.5 (CH), 90.2 (C), 80.0 (C), 35.1 (CH₂), 21.6 (CH₂); HRMS (ESI +ve) Exact mass calculated for C₁₂H₁₃ [M+H]⁺: 157.1012, found: 157.1012.

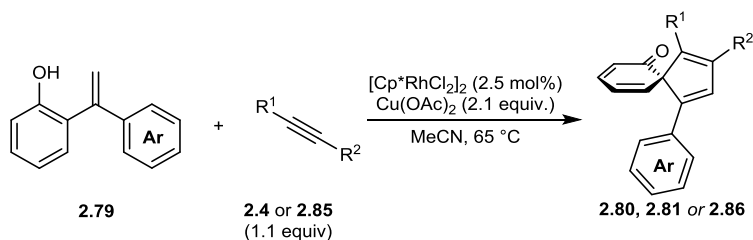


General Procedure D: Using Catalytic Copper



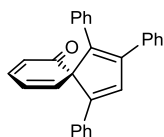
A stirred solution of the appropriate 2-alkenylphenol (0.50 mmol), $[\text{Cp}^*\text{RhCl}_2]_2$ (3.1 mg, 5.0 μmol), Cu(OAc)_2 (4.5 mg, 25 μmol) and the appropriate alkyne (0.60 mmol) in MeCN (2.0 mL) was heated at 85 $^\circ\text{C}$ under a balloon of air for the indicated time. The reaction mixture was cooled to room temperature, filtered through a short pad of silica using Et_2O (25 mL) as the eluent and concentrated *in vacuo*. Purification of the residue by flash column chromatography gave **2.80**, **2.81** or **2.86**.

General Procedure E: Using Stoichiometric Copper



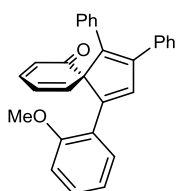
To a microwave vial, was added the appropriate 2-alkenylphenol (0.5 mmol), $[\text{Cp}^*\text{RhCl}_2]_2$ (7.7 mg, 13 μmol), Cu(OAc)_2 (191 mg, 1.05 mmol) and the appropriate alkyne (0.55 mmol). The vessel was then sealed and flushed with N_2 and MeCN (3 mL) was added. The reaction was then heated 65 $^\circ\text{C}$ for the indicated time. The reaction was cooled to room temperature, filtered through a short pad of silica using Et_2O (25 mL) as eluent and concentrated *in vacuo*. Purification of the residue by flash column chromatography gave product **2.80**, **2.81** or **2.86**.





1,2,4-Triphenylspiro[4.5]deca-1,3,7,9-tetraen-6-one (2.80c)

The title compound was prepared according to General Procedure D from 2-alkenylphenol **2.79c** (98 mg, 0.50 mmol) and diphenylacetylene **2.4a** (107 mg, 0.60 mmol) for a reaction time of 90 min and was purified by flash column chromatography (0 to 10% EtOAc/petroleum ether) to give spirotetraenone **2.80c** (155 mg, 83%) as a yellow foam. R_f 0.52 (20% EtOAc/petroleum ether); IR 2989, 2884, 1651 (C=O), 1620, 1545, 755, 640 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.48 (1H, s, ArC=CH), 7.34–7.27 (6H, m, $6 \times \text{CH=}$), 7.27–7.17 (7H, m, $7 \times \text{CH=}$), 7.14–7.08 (3H, m, $3 \times \text{CH=}$), 6.50 (1H, ddd, $J = 9.2, 6.0, 0.5$ Hz, O=CCH=CHCH=CH), 6.30 (1H, d, $J = 9.9$ Hz, O=CCH=CHCH=CH), 6.23 (1H, ddd, $J = 9.2, 1.8, 0.9$ Hz, O=CCH=CHCH=CH); ^{13}C NMR (125.8 MHz, CDCl_3) δ 196.4 (C), 148.1 (C), 145.6 (C), 142.9 (CH), 142.1 (C), 141.4 (CH), 134.8 (C), 134.8 (C), 134.0 (CH), 133.5 (CH), 129.2 ($2 \times \text{CH}$), 129.1 (CH), 128.7 ($2 \times \text{CH}$), 128.4 ($2 \times \text{CH}$), 128.2 ($2 \times \text{CH}$), 128.0 ($2 \times \text{CH}$), 127.60 (CH), 127.56 (CH), 125.6 ($2 \times \text{CH}$), 123.1 (CH), 99.7 (C), 75.3 (C); HRMS (ESI +ve) Exact mass calculated for $\text{C}_{28}\text{H}_{20}\text{NaO}$ $[\text{M}+\text{Na}]^+$: 395.1406, found: 395.1397; exact mass calculated for $\text{C}_{28}\text{H}_{21}\text{O}$ $[\text{M}+\text{H}]^+$: 373.1587, found: 373.1578.

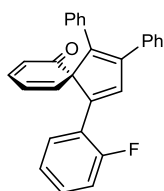


4-(2-Methoxyphenyl)-1,2-diphenylspiro[4.5]deca-1,3,7,9-tetraen-6-one (2.80d)

The title compound was prepared according to General Procedure D from 2-alkenylphenol **2.79d** (113 mg, 0.50 mmol) and diphenylacetylene **2.4a** (107 mg, 0.60 mmol) for a reaction time of 3.5 h and was purified by flash column chromatography (0 to 10% EtOAc/petroleum ether) to give spirotetraenone **2.80d** (156 mg, 76%) as an orange foam. R_f 0.40 (20% EtOAc/petroleum ether); IR 2989, 2884, 1663 (C=O), 1247, 1247, 750, 641 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.88 (1H, s, ArC=CH), 7.33–7.28 (2H, m, $2 \times \text{CH=}$), 7.25–7.16 (7H, m, $7 \times \text{CH=}$), 7.14–7.10 (2H, m, $2 \times \text{CH=}$), 7.00 (1H, ddd, $J = 9.8, 6.0, 1.8$ Hz, CH=), 6.94 (1H, dd, $J = 8.3, 0.7$ Hz, CH=), 6.84 (1H, td, $J = 7.4, 1.1$ Hz, CH=), 6.81 (1H, dd, $J = 7.8, 1.9$ Hz, CH=), 6.44 (1H, ddd, $J = 9.4, 6.1, 0.6$ Hz, CH=), 6.27–6.21 (2H, m, $2 \times \text{CH=}$), 3.91 (3H, s, OCH_3); ^{13}C NMR (125.8 MHz,



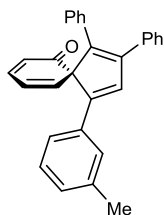
CDCl₃) δ 196.7 (C), 157.9 (C), 146.3 (C), 144.5 (C), 142.4 (CH), 141.8 (CH), 140.9 (C), 138.7 (CH), 135.1 (C), 134.9 (C), 129.6 (2 \times CH), 129.1 (CH), 128.5 (3 \times CH), 128.1 (CH), 128.0 (2 \times CH), 127.8 (2 \times CH), 127.4 (CH), 127.4 (CH), 122.8 (CH), 122.6 (C), 120.6 (CH), 111.0 (CH), 76.9 (C), 55.1 (CH₃); HRMS (ESI +ve) Exact mass calculated for C₂₉H₂₂NaO₂ [M+Na]⁺: 425.1512, found: 425.1518; exact mass calculated for C₂₉H₂₃O₂ [M+H]⁺: 403.1693, found: 403.1693.



4-(2-Fluorophenyl)-1,2-diphenylspiro[4.5]deca-1,3,7,9-tetraen-6-one (2.80e)

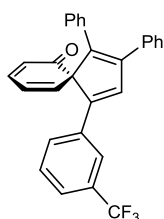
The title compound was prepared according to General Procedure D from 2-alkenylphenol **2.79e** (107 mg, 0.50 mmol) and diphenylacetylene **2.4a** (107 mg, 0.60 mmol) at 85 °C for a reaction time of 4 h and was purified by flash column chromatography (0 to 10% EtOAc/petroleum ether) to give spirotetraenone **2.80e** (164 mg, 84%) as a yellow foam. *R*_f 0.48 (20% EtOAc/petroleum ether); IR 3069, 2854, 1689 (C=O), 1731, 1566, 640, 654 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.74 (1H, d, *J* = 1.9 Hz, ArC=CH), 7.33–7.27 (2H, m, 2 \times ArH), 7.26–7.14 (7H, m, 7 \times ArH), 7.14–7.07 (3H, m, 3 \times ArH), 7.06 (1H, ddd, *J* = 9.9, 6.0, 1.6 Hz, O=CCH=CHCH=CH), 7.03–6.99 (1H, m, ArC=CH), 6.81 (1H, td, *J* = 8.0, 1.6 Hz, CH=), 6.49 (1H, ddd, *J* = 9.2, 6.0, 0.4 Hz, O=CCH=CHCH=CH), 6.27 (1H, d, *J* = 9.9 Hz, O=CCH=CHCH=CH), 6.22 (1H, ddd, *J* = 9.2, 1.6, 0.8 Hz, O=CCH=CHCH=CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 196.3 (C), 161.0 (d, *J* = 252.5 Hz, C), 146.1 (d, *J* = 1.2 Hz, C), 142.8 (CH), 141.9 (d, *J* = 1.9 Hz, C), 141.8 (d, *J* = 3.8 Hz, C), 141.0 (CH), 139.6 (d, *J* = 16.2 Hz, CH), 134.62 (C), 134.60 (C), 129.4 (2 \times CH), 129.1 (CH), 128.4 (2 \times CH), 128.4 (d, *J* = 9.0 Hz, CH), 128.2 (2 \times CH), 128.0 (d, *J* = 3.4 Hz, CH), 128.0 (2 \times CH), 127.7 (CH), 127.6 (CH), 124.3 (d, *J* = 3.5 Hz, CH), 123.3 (CH), 121.7 (d, *J* = 11.4 Hz, C), 116.2 (d, *J* = 26.2 Hz, CH), 76.3 (C); ¹⁹F NMR (376 MHz, CDCl₃) δ -109.9 (s); HRMS (ESI +ve) Exact mass calculated for C₂₈H₂₃FON [M+NH₄]⁺: 408.1758, found: 408.1743; exact mass calculated for C₂₈H₁₉FNaO [M+Na]⁺: 413.1312, found: 413.1302; exact mass calculated for C₂₈H₂₀FO [M+H]⁺: 391.1493, found: 391.1483.





4-(3-Methylphenyl)-1,2-diphenylspiro[4.5]deca-1,3,7,9-tetraen-6-one (2.80f)

The title compound was prepared according to General Procedure D from 2-alkenylphenol **2.79f** (105 mg, 0.50 mmol) and diphenylacetylene **2.4a** (107 mg, 0.60 mmol) for a reaction time of 3 h and was purified by flash column chromatography (0 to 10% EtOAc/petroleum ether) to give spirotetraenone **2.80f** (138 mg, 71%) as a brown oil. R_f 0.52 (20% EtOAc/petroleum ether); IR 3060, 2978, 2854, 1661 (C=O), 1602, 697, 640 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.44 (1H, s, ArC=CH), 7.33–7.26 (2H, m, 2 \times CH=), 7.25–7.13 (8H, m, 8 \times CH=), 7.12–7.05 (3H, m, 3 \times CH=), 7.05–7.00 (2H, m, 2 \times CH=), 6.46 (1H, ddd, J = 9.1, 6.0, 0.5 Hz, O=CCH=CHCH=CH), 6.28 (1H, dt, J = 9.7, 0.6 Hz, O=CCH=CHCH=CH), 6.20 (1H, ddd, J = 9.1, 1.8, 0.9 Hz, O=CCH=CHCH=CH), 2.29 (3H, s, CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ 196.4 (C), 148.2 (C), 145.6 (C), 142.8 (CH), 141.9 (C), 141.5 (CH), 138.1 (CH), 134.9 (C), 134.8 (C), 133.8 (C), 133.4 (C), 129.2 (2 \times CH), 129.0 (CH), 128.6 (CH), 128.40 (CH), 128.38 (2 \times CH), 128.1 (2 \times CH), 127.9 (2 \times CH), 127.6 (CH), 127.5 (CH), 126.3 (CH), 123.0 (CH), 122.7 (CH), 75.3 (C), 21.4 (CH_3); HRMS (ESI +ve) Exact mass calculated for $\text{C}_{29}\text{H}_{22}\text{NaO}$ $[\text{M}+\text{Na}]^+$: 409.1563, found: 409.1565; exact mass calculated for $\text{C}_{29}\text{H}_{23}\text{O}$ $[\text{M}+\text{H}]^+$: 387.1743, found: 387.1736.

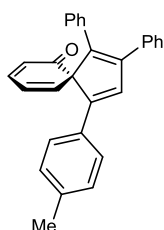


1,2-Diphenyl-4-[3-(trifluoromethyl)phenyl]spiro[4.5]deca-1,3,7,9-tetraen-6-one (2.80g)

The title compound was prepared according to General Procedure D from 2-alkenylphenol **2.79g** (132 mg, 0.50 mmol) and diphenylacetylene **2.4a** (107 mg, 0.60 mmol) for a reaction time of 4 h and was purified by flash column chromatography (0 to 10% EtOAc/petroleum ether) to give spirotetraenone **2.80g** (169 mg, 77%) as a yellow solid. R_f 0.48 (20% EtOAc/petroleum ether); m.p. >152–154 $^{\circ}\text{C}$ (decomp.) (Et_2O /petroleum ether); IR 2989, 2883, 1657 (C=O), 1625, 1165, 764, 641 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.62 (1H, s, ArC=CH), 7.59 (1H, s, CH=), 7.52–7.39 (3H, m, 3 \times CH=), 7.38–7.31



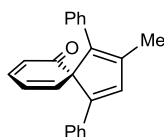
(2H, m, $2 \times \text{CH=}$), 7.31–7.19 (6H, m, $6 \times \text{CH=}$), 7.19–7.15 (3H, m, $3 \times \text{CH=}$), 6.59–6.53 (1H, m, CH=), 6.35 (1H, d, $J = 9.9$ Hz, O=CCH=CHCH=CH), 6.25 (1H, ddd, $J = 9.2, 1.7, 0.8$ Hz, O=CCH=CHCH=CH); ^{13}C NMR (100.6 MHz, CDCl_3) δ 195.9 (C), 146.4 (C), 145.4 (C), 143.2 (C), 143.0 (CH), 140.8 (CH), 135.7 (CH), 134.5 (C), 134.4 (C), 134.1 (C), 131.0 (q, $J = 32.8$ Hz, C), 129.2 (CH), 129.1 ($3 \times \text{CH}$), 128.5 (CH), 128.4 ($2 \times \text{CH}$), 128.2 ($2 \times \text{CH}$), 128.0 ($2 \times \text{CH}$), 127.8 ($2 \times \text{CH}$), 123.9 (q, $J = 3.6$ Hz, CH), 123.9 (q, $J = 272.6$ Hz, CF_3), 123.5 (CH), 122.2 (q, $J = 3.8$ Hz, CH), 75.1 (C); ^{19}F NMR (376 MHz, CDCl_3) δ –62.9 (s); HRMS (ESI +ve) Exact mass calculated for $\text{C}_{29}\text{H}_{23}\text{F}_3\text{NO}$ $[\text{M}+\text{NH}_4]^+$: 458.1726, found: 458.1727; exact mass calculated for $\text{C}_{29}\text{H}_{19}\text{F}_3\text{NaO}$ $[\text{M}+\text{Na}]^+$: 463.1280, found: 463.1280; exact mass calculated for $\text{C}_{29}\text{H}_{20}\text{F}_3\text{O}$ $[\text{M}+\text{H}]^+$: 441.1461, found: 441.1469.



4-(4-Methylphenyl)-1,2-diphenylspiro[4.5]deca-1,3,7,9-tetraen-6-one (2.80h).

The title compound was prepared according to General Procedure D from 2-alkenylphenol **2.79h** (105 mg, 0.50 mmol) and diphenylacetylene **2.4a** (107 mg, 0.60 mmol) for a reaction time of 2 h and was purified by flash column chromatography (0 to 10% EtOAc/petroleum ether) to give spirotetraenone **2.80h** (136 mg, 70%) as an orange foam. R_f 0.56 (20% EtOAc/petroleum ether); IR 2931, 2840, 1730 (C=O), 1531, 651, 641 cm^{-1} ; ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ 7.55 (1H, s, ArC=CH), 7.36–7.15 (H, m, $11 \times \text{CH=}$), 7.14–7.07 (4H, m, $4 \times \text{CH=}$), 6.53 (1H, ddd, $J = 9.2, 6.0, 0.4$ Hz, O=CCH=CHCH=CH), 6.22 (1H, ddd, $J = 9.2, 1.8, 0.8$ Hz, O=CCH=CHCH=CH), 6.17 (1H, d, $J = 9.9$ Hz, O=CCH=CHCH=CH), 2.28 (3H, s, CH_3); ^{13}C NMR (75.5 MHz, $(\text{CD}_3)_2\text{CO}$) δ 195.9 (C), 149.6 (C), 146.2 (C), 143.7 (CH), 143.0 (C), 142.1 (CH), 138.0 (C), 136.2 (C), 136.0 (C), 133.7 ($2 \times \text{CH}$), 132.2 (C), 130.1 ($3 \times \text{CH}$), 129.6 (CH), 129.2 ($2 \times \text{CH}$), 129.1 ($2 \times \text{CH}$), 128.8 ($2 \times \text{CH}$), 128.43 (CH), 128.36 (CH), 126.4 ($2 \times \text{CH}$), 124.1 (CH), 76.2 (C), 21.1 (CH_3); HRMS (ESI +ve) Exact mass calculated for $\text{C}_{29}\text{H}_{23}\text{O}$ $[\text{M}+\text{H}]^+$: 387.1743, found: 387.1787.

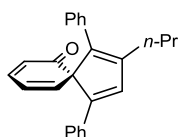




2-Methyl-1,4-diphenylspiro[4.5]deca-1,3,7,9-tetraen-6-one (2.81a)

Using catalytic copper: The title compound was prepared according to a modification of General Procedure D (in that the rhodium and copper loadings were increased) from 2-alkenylphenol **2.79c** (98 mg, 0.50 mmol, 20 mol%) and 1-phenyl-1-propyne **2.4b** (70 mg, 0.60 mmol) at 85 °C for a reaction time of 3 h and was purified by flash column chromatography (0 to 10% EtOAc/petroleum ether) to give spirotetraenone **2.81a** (78 mg, 51%) as an orange solid.

Using stoichiometric copper: The title compound was prepared according to a modification of General Procedure E (in that 1.2 equiv of alkyne was used) from 2-alkenylphenol **2.79c** (98 mg, 0.50 mmol) and 1-phenyl-1-propyne **2.4b** (70 mg, 0.60 mmol) for a reaction time of 1 h and was purified by flash column chromatography (0 to 10% EtOAc/petroleum ether) to give spirotetraenone **2.81a** (119 mg, 76%) as an orange solid. R_f 0.69 (50% EtOAc/petroleum ether); m.p. 122–124 °C (Et₂O/petroleum ether); IR 2900, 2840, 1657 (C=O), 757, 641 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.29–7.20 (7H, m, 7 \times ArH), 7.19–7.11 (3H, m, 3 \times ArH), 7.10 (1H, s, ArC=CH), 7.07 (1H, ddd, J = 9.8, 6.0, 1.9 Hz, O=CCH=CHCH=CH), 6.41 (1H, ddd, J = 9.2, 6.0, 0.5 Hz, O=CCH=CHCH=CH), 6.28 (1H, d, J = 9.8 Hz, O=CCH=CHCH=CH), 6.10 (1H, ddd, J = 9.2, 1.9, 0.8 Hz, O=CCH=CHCH=CH), 2.03 (3H, s, CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 196.9 (C), 147.5 (C), 143.0 (CH), 143.0 (C), 142.2 (C), 142.1 (CH), 135.7 (CH), 134.5 (C), 133.4 (C), 128.9 (CH), 128.8 (2 \times CH), 128.5 (2 \times CH), 127.8 (2 \times CH), 127.3 (CH), 127.2 (CH), 125.4 (2 \times CH), 122.5 (CH), 74.4 (C), 14.1 (CH₃); HRMS (ESI +ve) Exact mass calculated for C₂₃H₁₈NaO [M+Na]⁺: 333.1250, found: 333.1248; exact mass calculated for C₂₃H₁₉O [M+H]⁺: 311.1430, found: 311.1421.

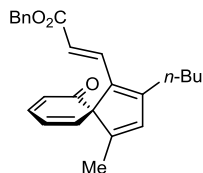


1,4-Diphenyl-2-propylspiro[4.5]deca-1,3,7,9-tetraen-6-one (2.81b)

The title compound was prepared according to a modification of General Procedure E (in that 1.2 equiv. of alkyne was used) from 2-alkenylphenol



2.79c (98 mg, 0.50 mmol) and 1-phenyl-1-pentyne **2.4c** (86 mg, 0.60 mmol) for a reaction time of 1 h and was purified by flash column chromatography (0 to 50% CH₂Cl₂/petroleum ether) to give spirotetraenone **2.81b** (101 mg, 60%) as an orange solid. *R*_f 0.32 (50% CH₂Cl₂/petroleum ether); m.p. 98–100 °C (Et₂O/petroleum ether); IR 2989, 2954, 1659 (C=O), 1546, 758, 706 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.32–7.23 (7H, m, 7 × CH=), 7.22–7.17 (2H, m, 2 × CH=), 7.16–7.10 (2H, m, 2 × CH=), 7.07 (1H, ddd, *J* = 9.8, 6.0, 1.9 Hz, O=CCH=CHCH=CH), 6.44 (1H, ddd, *J* = 9.1, 6.0, 0.7 Hz, O=CCH=CHCH=CH), 6.27 (1H, dt, *J* = 9.8, 0.7 Hz, O=CCH=CHCH=CH), 6.14 (1H, ddd, *J* = 9.1, 1.9, 0.7 Hz, O=CCH=CHCH=CH), 2.41–2.25 (2H, m, CH₂CH₂CH₃), 1.73–1.53 (2H, m, CH₂CH₃), 0.94 (3H, t, *J* = 7.4 Hz, CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 196.9 (C), 147.6 (C), 147.6 (C), 142.9 (CH), 142.2 (C), 142.0 (CH), 134.5 (C), 133.9 (CH), 133.6 (C), 129.3 (2 × CH), 128.9 (CH), 128.6 (2 × CH), 127.7 (2 × CH), 127.4 (CH), 127.2 (CH), 125.5 (2 × CH), 122.6 (CH), 74.8 (C), 29.8 (CH₂), 22.4 (CH₂), 13.8 (CH₃); HRMS (ESI +ve) Exact mass calculated for C₂₅H₂₂NaO [M+Na]⁺: 361.1563, found: 361.1596; exact mass calculated for C₂₅H₂₃O [M+H]⁺: 393.1743, found: 339.1750.

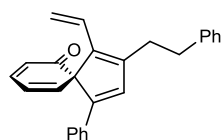


Benzyl (E)-3-[2-butyl-4-methyl-10-oxospiro[4.5]deca-1,3,6,8-tetraen-1-yl]prop-2-enoate (2.86j**)**

The title compound was prepared according to General Procedure E from 2-alkenylphenol **2.79b** (67 mg, 0.50 mmol) and enyne **2.85c** (133 mg, 0.55 mmol) for a reaction time of 20 min and was purified by flash column chromatography (0 to 10% EtOAc/petroleum ether) to give spirotetraenone **2.86j** (153 mg, 82%) as an orange oil. *R*_f 0.42 (20% EtOAc/petroleum ether); IR 2989, 2956, 1708 (C=O), 1664 (C=O), 1597, 1156, 640 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.57 (1H, d, *J* = 15.7 Hz, BnO₂CCH=CH), 7.38–7.35 (4H, m, 4 × CH=), 7.34–7.25 (2H, m, 2 × CH=), 6.53 (1H, ddd, *J* = 9.0, 6.2, 0.5 Hz, O=CCH=CHCH=CH), 6.37–6.31 (2H, m, 2 × CH=), 5.80 (1H, ddd, *J* = 9.2, 1.8, 0.8 Hz, O=CCH=CHCH=CH), 5.17 (1H, d, *J* = 12.6 Hz, OCH_AH_B), 5.15 (1H, d, *J* = 15.7 Hz, BnO₂CCH=CH), 5.14 (1H, d, *J* = 12.6 Hz, OCH_AH_B), 2.64–2.48 (2H, m, CH₂CH₂CH₂CH₃), 1.77 (3H, t, *J* = 1.5 Hz, =CCH₃), 1.65–1.46 (2H, m,



$\text{CH}_2\text{CH}_2\text{CH}_3$), 1.43–1.32 (2H, m, CH_2CH_3), 0.94 (3H, t, $J = 7.4$ Hz, CH_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ 196.3 (C), 167.2 (C), 159.0 (C), 150.3 (C), 143.3 (CH), 142.1 (CH), 138.4 (C), 136.3 (C), 135.1 (CH), 134.9 (CH), 128.4 ($2 \times \text{CH}$), 128.2 ($2 \times \text{CH}$), 128.1 (CH), 127.9 (CH), 122.7 (CH), 114.2 (CH), 73.1 (C), 65.8 (CH_2), 31.2 (CH_2), 27.5 (CH_2), 22.3 (CH_2), 13.8 (CH_3), 12.7 (CH_3); HRMS (ESI +ve) Exact mass calculated for $\text{C}_{25}\text{H}_{26}\text{NaO}_3$ $[\text{M}+\text{Na}]^+$: 397.1774, found: 397.1772; exact mass calculated for $\text{C}_{25}\text{H}_{27}\text{O}_3$ $[\text{M}+\text{H}]^+$: 375.1955, found: 375.1959.



1-Ethenyl-4-phenyl-2-(2-phenylethyl)spiro[4.5]deca-1,3,7,9-tetraen-6-one (2.86l)

The title compound was prepared according to General Procedure E from 2-alkenylphenol **2.79b** (98 mg, 0.50 mmol) and enyne **2.85d** (86 mg, 0.55 mmol) for a reaction time of 20 min and was purified by flash column chromatography (0 to 10% EtOAc/petroleum ether) to give spirotetraenone **2.86l** (146 mg, 87%) as an orange oil. R_f 0.22 (10% EtOAc/petroleum ether); IR 3026, 2924, 1663 ($\text{C}=\text{O}$), 1663, 1546, 1493, 1242, 759 cm^{-1} ; ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ 7.42 (1H, d, $J = 9.9, 6.1, 1.8$ Hz, $\text{O}=\text{CCH}=\text{CHCH}=\text{CH}$), 7.35–7.14 (11H, m, $11 \times \text{CH}=\text{}$), 6.55 (1H, $J = 9.2, 6.1, 0.6$ Hz, $\text{O}=\text{CCH}=\text{CHCH}=\text{CH}$), 6.45–6.35 (2H, m, $2 \times \text{CH}=\text{}$), 5.94 (1H, ddd, $J = 9.2, 1.8, 0.9$ Hz, $\text{O}=\text{CCH}=\text{CHCH}=\text{CH}$), 4.87 (1H, dd, $J = 3.5, 0.7$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}=\text{}$), 4.83 (1H, dd, $J = 9.6, 0.8$ Hz, $\text{CH}_\text{A}\text{H}_\text{B}=\text{}$), 2.99–2.89 (2H, m, CH_2), 2.88–2.73 (2H, CH_2); ^{13}C NMR (100.6 MHz, $(\text{CD}_3)_2\text{CO}$) δ 195.6 (C), 150.0 (C), 149.5 (C), 145.0 (CH), 143.5 (CH), 143.3 (C), 142.1 (C), 136.0 (CH), 134.8 (C), 129.50 (CH), 129.47 ($2 \times \text{CH}$), 129.3 ($2 \times \text{CH}$), 129.1 ($2 \times \text{CH}$), 128.3 (CH), 128.2 (CH), 126.8 (CH), 126.2 ($2 \times \text{CH}$), 122.9 (CH), 113.4 (CH_2), 72.0 (C), 36.0 (CH_2), 30.2 (CH_2); HRMS (ESI +ve) Exact mass calculated for $\text{C}_{26}\text{H}_{22}\text{NaO}$ $[\text{M}+\text{Na}]^+$: 373.1563, found: 373.1580; Exact mass calculated for $\text{C}_{26}\text{H}_{23}\text{O}$ $[\text{M}+\text{H}]^+$: 351.1743, found: 351.1750.



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